(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 669 317 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
04.09.2002 Bulletin 2002/36

(21) Application number: **95101059.4**

(22) Date of filing: **26.01.1995**

(51) Int Cl.[7]: **C07D 207/16**, C07D 211/60, C07D 403/06, C07D 403/12, C07D 401/12, C07D 403/08, C07D 403/10, C07K 5/06, A61K 31/40

(54) Prolineamide derivatives

Prolineamid-Derivate

Dérivés de la prolinamide

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
LT SI

(30) Priority: **27.01.1994 JP 773394**

(43) Date of publication of application:
30.08.1995 Bulletin 1995/35

(73) Proprietor: **Mitsubishi Chemical Corporation**
Chiyoda-ku, Tokyo (JP)

(72) Inventors:
- **Ohshima, Masahiro, Mitsubishi Chemical Corp.**
  Aoba-ku, Yokohama-shi, Kanagawa-ken (JP)
- **Iwase, Norimichi, Mitsubishi Chemical Corp.**
  Aoba-ku, Yokohama-shi, Kanagawa-ken (JP)
- **Sugiyama, Shigeo, Mitsubishi Chemical Corp.**
  Aoba-ku, Yokohama-shi, Kanagawa-ken (JP)
- **Sugawara, Koichi, Mitsubishi Chemical Corp.**
  Aoba-ku, Yokohama-shi, Kanagawa-ken (JP)
- **Okitsu, Misao, Mitsubishi Chemical Corp.**
  Aoba-ku, Yokohama-shi, Kanagawa-ken (JP)
- **Tamao, Yoshikuni, Mitsubishi Chemical Corp.**
  Aoba-ku, Yokohama-shi, Kanagawa-ken (JP)
- **Morinaka, Yasuhiro, Mitsubishi Chemical Corp.**
  Aoba-ku, Yokohama-shi, Kanagawa-ken (JP)

(74) Representative:
Hansen, Bernd, Dr. Dipl.-Chem. et al
Hoffmann Eitle,
Patent- und Rechtsanwälte,
Arabellastrasse 4
81925 München (DE)

(56) References cited:
EP-A- 0 601 459 **WO-A-93/15756**
US-A- 5 153 176

- **CHEMICAL ABSTRACTS, vol. 104, no. 7, 17 February 1986, Columbus, Ohio, US; abstract no. 47665b, & SYMP. BIOL. HUNG. (PROTEINASE ACTION), vol.25, 1984, BUDAPEST pages 277 - 298 S. BAJUSZ & CAS REGISTRY HANDBOOK 1986 SUPPL. (STN DATABASE)**
- **CHEMICAL ABSTRACTS, vol. 103, no. 3, 22 July 1985, Columbus, Ohio, US; abstract no. 18900y, & BIOCHEMISTRY, vol.24, no.13, 1985, EASTON, PA US pages 3149 - 3157 C.F. VENCILL ET AL.**
- **CHEMICAL ABSTRACTS, vol. 92, no. 3, 21 January 1980, Columbus, Ohio, US; abstract no. 17850z, & BIOORG. CHEM., vol.8, no.3, 1979 pages 299 - 309 C.H. HASSALL ET AL.**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 0 669 317 B1

Description

FIELD OF THE INVENTION

[0001] The present invention relates to novel proline derivatives. More particularly, it relates to proline derivatives having a protease inhibition activity or pharmaceutically acceptable salts thereof and protease inhibitors containing the same as an active ingredient.

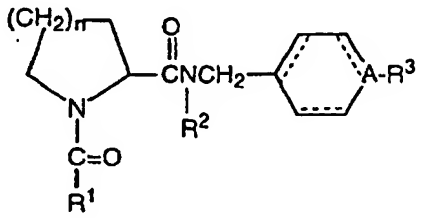
BACKGROUND OF THE INVENTION

[0002] It has been known that various proteases are present in the living body, for example, a group of serine proteases such as thrombin, factor Xa, factor IXa, factor VIIa, trypsin, plasmin, tissue plasminogen activator, kallikrein, C3/C5 convertase in the complement system, tryptase, etc. is known. Further, it is also known that these proteases cause various diseases when they are activated abnormally by some reason. Accordingly, substances which inhibit the activity of these proteases are useful as a clinical remedy. For example, antithrombin agents, anti-factor Xa agents and anti-factor VIIa agents are useful for treating thrombosis, antitrypsin agents are useful for treating pancreatitis, antiplasmin agents are useful as hemostatics, antiallergic agents and antiinflammatory agents, antikallikrein agents are useful as a remedy for inflammation and ulcer, and anticomplementary agents are useful as a remedy for nephritis and rheumatoid arthritis. Protease inhibitors having these actions have hitherto been developed, but they are not necessarily sufficient for practical use in view of protease inhibition activity, stability in the living body and the like. For example, tripeptide derivatives consist of arginine derivatives are known as protease inhibitors. That is, D-phenylalanyl-L-prolyl-L-arginal is known as a thrombin inhibitor (e.g. Folia Haematol., 109, 22 (1982)) but is fairly unstable in the living body (J. Med. Chem., 33, 1729 (1990)). Further, arginal derivatives (Japanese Laid-open Patent Publication No. 4-89498) or amidinophenylalanine derivatives (Thromb. Res., 17, 425 (1980)) are reported as protease inhibitors but their inhibition activity is low.

[0003] Under these circumstances, the present inventors have studied to develop structurally novel drugs having enzyme inhibition activity and stability in vivo, which are sufficient for practical use. As a result, it has been found that certain prolineamide derivatives can attain the desired object, thus the present invention has been established.

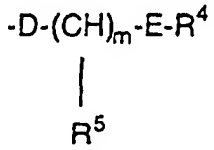
SUMMARY OF THE INVENTION

[0004] That is, the present invention provides a prolineamide derivative represented by the formula (I):



(I)

wherein A is a carbon atom or a nitrogen atom; n is an integer of 0 to 2; a broken line is absent or a single bond; R^1 is



{wherein D and E independently indicate a single bond or an optionally branched C_1-C_6 alkylene group;

R^4 is a C_1-C_6 alkyl group, -OR^6 (R^6 is a hydrogen atom, a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyl group), -SR^7 (R^7 is a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group

or an optionally substituted C_7-C_{12} aralkyl group), -SOR^8 (R^8 is an optionally substituted C_6-C_{10} aryl group or an optionally substituted C_3-C_8 cycloalkyl group), -SO_2R^9 (R^9 is an optionally substituted C_6-C_{10} aryl group or an optionally substituted C_3-C_8 cycloalkyl group), -COR^{10} (R^{10} is a hydroxyl group, a C_1-C_6 alkoxy group, an optionally substituted C_6-C_{10} aryl group or an optionally substituted C_3-C_8 cycloalkyl group), -NHR^{11} (R^{11} is a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyl group), -$NHCOR^{12}$ (R^{12} is a C_1-C_6 alkoxy group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyloxy group), -$NHSO_2R^{13}$ (R^{13} is a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group, an optionally substituted C_7-C_{12} aralkyl group, an optionally substituted 5- to 10-membered heterocyclic group), an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group, an optionally substituted 5- to 10-membered heterocyclic group or -$SiR^{14}R^{15}R^{16}$ (R^{14}, R^{15}, and R^{16} independently indicate a C_1-C_6 alkyl group);

R^5 is a -OR^{17} (R^{17} is a hydrogen atom, -$SiR^{22}R^{23}R^{24}$ (R^{22}, R^{23}, and R^{24} independently indicate a C_1-C_6 alkyl group), a C_1-C_6 alkyl group or an optionally substituted 5- to 10-membered heterocyclic group)), -$OCOR^{18}$ (R^{18} is a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, an amino group, a C_1-C_6 alkylamino group, a C_2-C_{12} dialkylamino group or a C_2-C_7 alkenylamino group), -NHR^{19} (R^{19} is a hydrogen atom, a C_1-C_6 alkyl group or an optionally substituted C_7-C_{12} aralkyl group), -$NHCOR^{20}$ (R^{20} is a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_6 haloalkyl group, a C_1-C_6 alkoxy group, an optionally substituted C_3-C_8 cycloalkyl group, a C_2-C_7 carboxyalkyloxy group, a C_2-C_7 alkenyloxy group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_6-C_{10} aryloxy group, a C_3-C_9 alkoxycarbonylalkoxy group, a C_2-C_{12} dialkylamino group or an optionally substituted C_7-C_{12} aralkyloxy group) or -$NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group, a C_1-C_6 haloalkyl group, a C_2-C_7 carboxyalkyl group, an optionally substituted C_6-C_{10} aryl group, a C_3-C_9 alkoxycarbonylalkyl group or an optionally substituted C_7-C_{12} aralkyl group); and m is 0 or 1};

each of said 5- to 10-membered heterocyclic groups is independently selected from a furan ring, a tetrahydrofuran ring, a pyran ring, a benzofuran ring, a chroman ring, a thiophene ring, a benzothiophene ring, a pyrrole ring, an imidazole ring, a pyrazole ring, a triazole ring, a pyridine ring, a piperidine ring, a pyrazine ring, a piperazine ring, a pyrimidine ring, an indole ring, a benzimidazole ring, a purine ring, a quinoline ring, a phthalazine ring, a quinazoline ring, a cinnoline ring, an oxazole ring, a thiazole ring and a morpholine ring;

each of said optional substituents being independently selected from C_1-C_6 alkyl group, a C_1-C_6 haloalkyl group, a C_1-C_6 alkoxy group, a hydroxyl group, a carboxyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 carboxyalkyloxy group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkoxycarbonyloxy group, a C_8-C_{13} aralkyloxycarbonyl group, a C_3-C_9 alkoxycarboxyalkoxy group and a halogen atom);

R^2 is a hydrogen atom or a C_1-C_6 alkyl group; and R^3 is -$C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom or a hydroxyl group) or -NH_2; provided that R^3 is -$C(=NR^{25})NH_2$ (R^{25} is as defined above) when A is a nitrogen atom, or a salt or hydrate thereof;

with the proviso that if the substituent R^2 represents a hydrogen atom, the group "D" represents a single bond, and the index n is 1 or 2, then neither of the substituents R^4 or R^5 represents a group including an aminosulfonyl moiety;

and pharmaceutical use thereof.

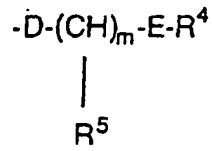
DETAILED DESCRIPTION OF THE INVENTION

[0005] The prolineamide derivative of the present invention is represented by the above formula (I). Examples of the optionally branched C_1-C_6 alkylene group in the above definition include -CH_2-, -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -$CH(CH_3)CH_2$-, -$CH_2CH(CH_3)$-, -$C(CH_3)_2CH_2$-, -$CH_2C(CH_3)_2$-, -$CH(CH_3)CH(CH_3)$- and the like. Examples of the C_1-C_6 alkyl group include methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, s-butyl group, i-butyl group, t-butyl group, n-pentyl group, n-hexyl group and the like. Examples of the C_1-C_3 alkyl group include those having three carbon atoms or less among those illustrated above. Examples of the C_1-C_6 alkoxy group include methoxy group, ethoxy group, n-propoxy group, i-propoxy group, n-butyloxy group, s-butyloxy group, i-butyloxy group, t-butyloxy group, n-pentyloxy group, n-hexyloxy group and the like. Examples of the C_2-C_7 alkoxycarbonyl group include methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, i-propoxycarbonyl group, n-butyloxycarbonyl group, t-butyloxycarbonyl group, n-pentyloxycarbonyl group, n-hexyloxycarbonyl group and the like. Examples of the C_3-C_8 cycloalkyl group include cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group and the like. Examples of the C_6-C_{10} aryl group include phenyl group, tolyl group, naphthyl group and the like. Examples of the C_7-C_{12} aralkyl group include benzyl group, phenylethyl group, phenylpropyl group, naphthylmethyl group and the like. Examples of the C_6-C_{10} aryloxy group include phenyloxy group, naphthyloxy group and the like. Examples of the C_7-C_{12} aralkyloxy group include benzyloxy group, phenylethyloxy group, phenylpropyloxy group, naphthylmethyloxy group and the like. Examples of the C_1-C_6 haloalkyl group include chloromethyl group, bromomethyl group, dichloromethyl group, 1-chloroethyl group, 2-chloroethyl group, 3-chloropropyl group, 4-chlorobutyl group, 5-chloropentyl group, 6-chlorohexyl group, difluoromethyl group, trifluoromethyl group and the like. Examples of the C_2-C_7 carboxyalkyl group include carboxymethyl group,

2-carboxyethyl group, 3-carboxypropyl group, 4-carboxybutyl group, 5-carboxypentyl group, 6-carboxyhexyl group and the like. Examples of the C_2-C_7 carboxyalkyloxy group include carboxymethoxy group, 2-carboxyethoxy group, 3-carboxypropoxy group, 4-carboxybutyloxy group, 5-carboxypentyloxy group, 6-carboxyhexyloxy group and the like. Examples of the C_2-C_7 alkenyloxy group include vinyloxy group, aryloxy group, 2-propenyloxy group, isopropenyloxy group, 3-butenyloxy group, 4-pentenyloxy group, 5-hexenyloxy group and the like. Examples of the C_2-C_7 alkenylamino group include vinylamino group, arylamino group, 2-propenylamino group, Isopropenylamino group, 3-butenylamino group, 4-pentenylamino group, 5-hexenylamino group and the like. Examples of the C_1-C_6 alkylamino group include methylamino group, ethylamino group, n-propylamino group, n-butylamino group and the like. Examples of the C_2-C_{12} dialkylamino group include dimethylamino group, methylethylamino group, diethylamino group, di-n-propylamino group and the like. Examples of the C_2-C_7 acyl group include acetyl group, propionyl group, butyryl group, isobutyryl group, valeryl group, isovaleryl group, pivaroyl group, hexanoyl group, heptanoyl group and the like. Examples of the C_2-C_7 acyloxy group include acetyloxy group, propionyloxy group, butyryloxy group, isobutyryloxy group, valeryloxy group, isovaleryloxy group, pivaroyloxy group, hexanoyloxy group, heptanoyloxy group and the like. Examples of the C_2-C_7 alkokycarbonyloxy group include methoxycarbonyloxy group, ethoxycarbonyloxy group, n-propoxycarbonyloxy group, n-butyloxycarbonyloxy group, n-pentyloxycarbonyloxy group, n-hexyloxycarbonyloxy group and the like. Examples of the C_2-C_7 hydroxyalkylcarbonyloxy group include hydroxymethylcarbonyloxy group, 2-hydroxyethylcarbonyloxy group, 3-hydroxypropylcarbonyloxy group, 4-hydroxybutylcarbonyloxy group, 5-hydroxypentylcarbonyloxy group, 6-hydroxyhexylcarbonyloxy group and the like. Examples of the C_3-C_9 alkoxycarbonylalkoxy group include methoxycarbonylmethoxy group, ethoxycarbonylmethoxy group, propoxycarbonylmethoxy group, methoxycarbonylethoxy group, ethoxycarbonylethoxy group, propoxycarbonylethoxy group and the like. Examples of the C_3-C_9 alkoxycarbonylalkyl group include methoxycarbonylmethyl group, ethoxycarbonylmethyl group, propoxycarbonylmethyl group, methoxycarbonylethyl group, methoxycarbonylmethyl group, propoxycarbonylethyl group and the like. Examples of the above "optional substituents" include those given above for the respective group of compounds. Examples of the C_8-C_{13} aralkyloxycarbonyl group include benzyloxycarbonyl group, phenylethyloxycarbonyl group, phenylproplyloxycarbonyl group, naphthylmethyloxycarbonyl group, etc. Examples of the halogen atom include fluorine atom, chlorine atom, bromine atom and the like.

[0006] In the compound represented by the above formula (I) of the present invention, a carbon atom is preferred as A.

[0007] Examples of preferred compounds of the present invention include those of the formula (I), wherein A is a carbon atom; n is 1 or 2; R^1 is



(wherein D and E independently indicate a single bond or an optionally branched C_1-C_6 alkylene group;

R^4 is a C_1-C_6 alkyl group: -OR^6 (R^6 is a C_1-C_6 alkyl group; a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; or a C_7-C_{12} aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group): -SR^7 (R^7 is a C_1-C_6 alkyl group, a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; or a C_7-C_{12} aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group): -COOH: a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group: a C_3-C_8 cycloalkyl group:

or $-SiR^{14}R^{15}R^{16}$ (R^{14}, R^{15}, and R^{16} independently indicate a C_1-C_6 alkyl group);

R^5 is -OH, $-OCOR^{18}$ (R^{18} is a C_1-C_6 alkoxy group or a C_2-C_7 alkenylamino group), $-NH_2$, $-NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group, a C_6-C_{10} aryloxy group, a C_3-C_9 alkoxycarbonylalkoxy group, a C_2-C_{12} dialkylamino group or a C_7-C_{12} aralkyloxy group) or $-NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group, a C_2-C_7 carboxyalkyl group, a C_6-C_{10} aryl group, a C_3-C_9 alkoxycarbonylalkyl group or a C_7-C_{12} aralkyl group); and m is 0 or 1}; and

R^2 is a hydrogen atom.

[0008] As the more preferred compound of the present invention, there is a compound of the formula (I), wherein A is a carbon atom; n is 1; R^1 is

{wherein D arid E independently indicate a single bond or an optionally branched C_1-C_6 alkylene group;

R^4 is a C_1-C_6alkyl group; $-OR^6$ (R^6 is a C_6-C_{10} aryl or C_7-C_{12} aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group); $-SR^7$ (R^7 is a C_1-C_6 alkyl group); a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group; or a C_3-C_6 cycloalkyl group;

R^5 is -OH, $-NH_2$, $-NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group or a C_7-C_{12} aralkyloxy group) or $-NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group or a C_6-C_{10} aryl group);

and m is 1}; and

R^2 is a hydrogen atom.

[0009] As the more preferred compound of the present invention, there is a compound of the formula (I), wherein A is a carbon atom; n is 1; R^1 is

{wherein D is a single bond and E is a single bond or a C_1-C_6 alkylene group;

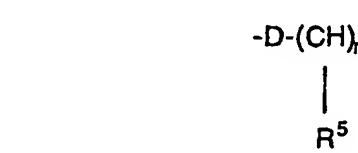
R^4 is a C_1-C_6 alkyl group; $-OR^6$ (R^6 is a C_6-C_{10} aryl or C_7-C_{12} aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group); $-SR^7$ (R^7 is a C_1-C_6 alkyl group); a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group; or a C_3-C_6 cycloalkyl group;

R^5 is $-NH_2$, $-NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group or a C_7-C_{12} aralkyloxy group) or $-NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group or a C_6-C_{10} aryl group);

and m is 1}; and

R^2 is a hydrogen atom.

[0010] As the still more preferred compound of the present invention, there is a compound of the formula (I), wherein A is a carbon atom; n is 1; R^1 is

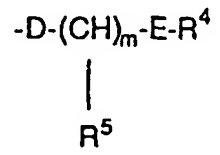


(wherein D is a single bond; E is a single bond or a C_1-C_3 alkylene group; R^4 is a C_3-C_6 alkyl group, $-OR^6$ (R^6 is a C_1-C_6 alkyl group), a phenyl group or a C_3-C_6 cycloalkyl group; R^5 is -OH, $-NHR^{19}$ (R^{19} is a hydrogen atom), $-NHCOR^{20}$

(R^{20} is a C_1-C_6 alkoxy group) or $-NHSO_2R^{21}$ (R^{21} is a C_1-C_3 alkyl group); and m is 1}; and

R^2 is a hydrogen atom.

[0011] As the particularly preferred compound of the present invention, there is a compound of the formula (I), wherein A is a carbon atom; n is 1; R^1 is



{wherein D is a single bond; E is a single bond or a C_1-C_6 alkylene group; R^4 is a C_1-C_6 alkyl group; R^5 is $-NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group); and mis 1};

R^2 is a hydrogen atom; and

R^3 is $-C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom or a hydroxyl group)).

[0012] As the most preferred compound of the present invention, there is trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 461 in Table 1 in Example 33).

[0013] The prolineamide derivatives represented by the above formula (I) can afford various stereoisomers. For example, concerning asymmetric carbon atoms, the absolute configuration may be D-configuration, L-configuration or DL configuration and all types thereof are included in the compounds of the present invention.

[0014] Examples of the salt which can be formed with the compounds of the above formula (I) of the present invention include inorganic acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.; organic acid salts such as succinate, oxalate, fumarate, maleate, lactate, tartrate, citrate, acetate, glycolate, methanesulfonate, toluenesulfonate, etc. Further, the proline derivatives of the above formula (I) containing a free carboxyl group can also form a salt with a pharmaceutically acceptable base.

[0015] Examples of the salt include alkaline metal salt, alkaline earth metal salt, ammonium salt, alkyl ammonium salt and the like.

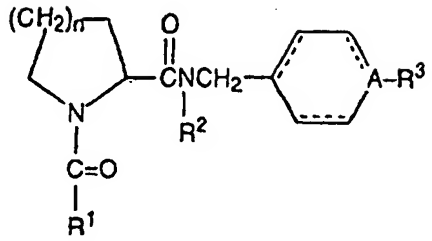
[0016] Further, the prolineamide derivatives of the above formula (I) and the salts thereof can also form a hydrate.

[0017] Hereinafter, examples of the compounds of the present invention will be described.

[0018] The following compounds were deleted during prosecution;

77-81, 104, 106-110, 112-163, 165-172, 230-233, 237, 239, 241, 243, 245-246, 250-253, 269-270, 274, 276, 283-284, 291-293, 295, 302-305, 317, 319, 321, 324, 326, 328, 382, 398-399, 437-442, 452, 501-504, 510, 515-746, 751, 759-760, 772-775, 788-792, 805-815, 820, 828-829, 834, 898-971, 973-976, 996-1002, 1004-1006. Compounds No. 105 and 776 were designated as Reference compounds.

Table 1



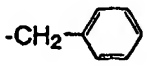
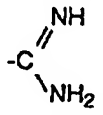
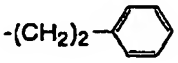
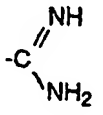
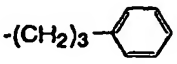
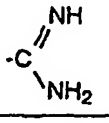
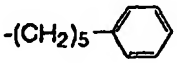
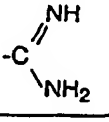
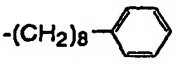
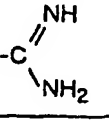
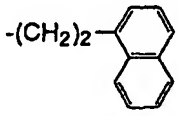
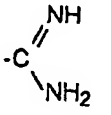
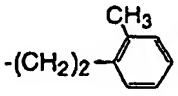
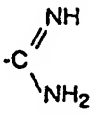
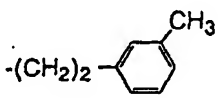
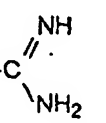
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
1		-H		1	C	Single bond
2		-H		1	C	Single bond
3		-H		1	C	Single bond
4		-H		1	C	Single bond
5		-H		1	C	Single bond
6		-H		1	C	Single bond
7		-H		1	C	Single bond
8		-H		1	C	Single bond

Table 1 (continued)

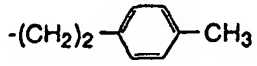
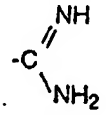
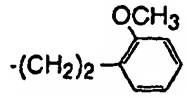
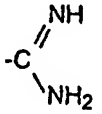
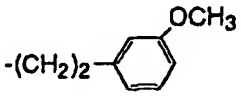
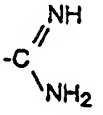
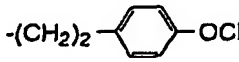
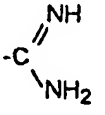
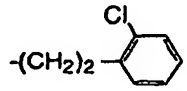
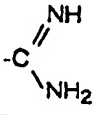
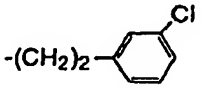
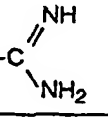
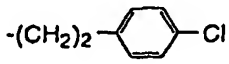
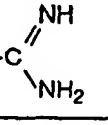
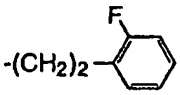
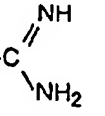
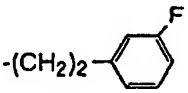
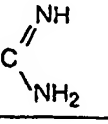
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4\right)$ with R^5	$-R^2$	$-R^3$	n	A	Broken line
9		-H		1	C	Single bond
10		-H		1	C	Single bond
11		-H		1	C	Single bond
12		-H		1	C	Single bond
13		-H		1	C	Single bond
14		-H		1	C	Single bond
15		-H		1	C	Single bond
16		-H		1	C	Single bond
17		-H		1	C	Single bond

Table 1 (continued)

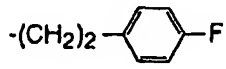
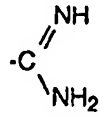
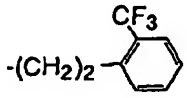
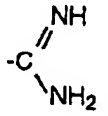
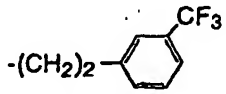
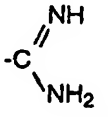
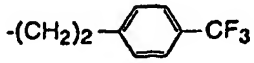
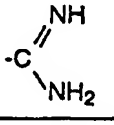
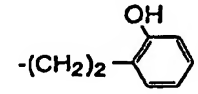
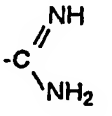
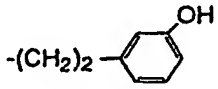
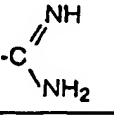
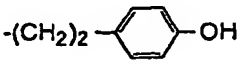
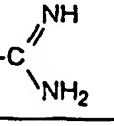
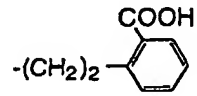
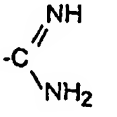
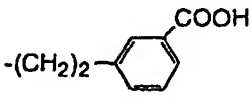
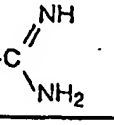
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
18		-H		1	C	Single bond
19		-H		1	C	Single bond
20		-H		1	C	Single bond
21		-H		1	C	Single bond
22		-H		1	C	Single bond
23		-H		1	C	Single bond
24		-H		1	C	Single bond
25		-H		1	C	Single bond
26		-H		1	C	Single bond

Table 1 (continued)

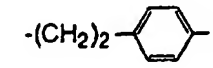
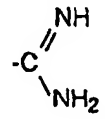
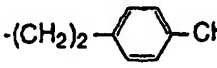
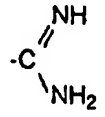
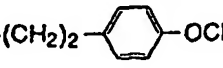
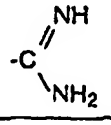
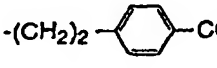
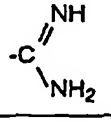
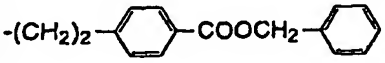
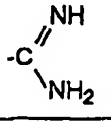
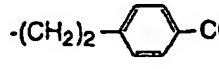
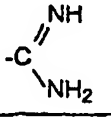
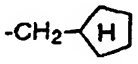
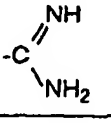
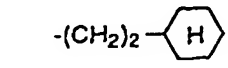
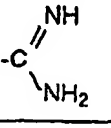
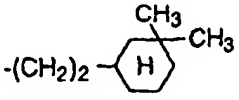
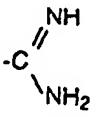
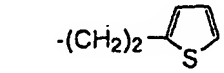
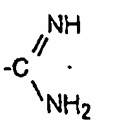
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	-R2	-R3	n	A	Broken line
27		-H		1	C	Single bond
28		-H		1	C	Single bond
29		-H		1	C	Single bond
30		-H		1	C	Single bond
31		-H		1	C	Single bond
32		-H		1	C	Single bond
33		-H		1	C	Single bond
34		-H		1	C	Single bond
35		-H		1	C	Single bond
36		-H		1	C	Single bond

Table 1 (continued)

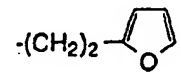
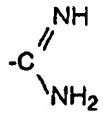
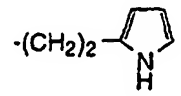
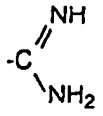
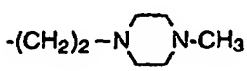
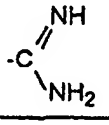
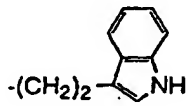
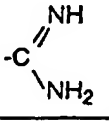
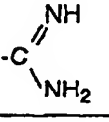
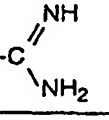
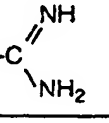
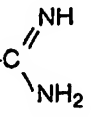
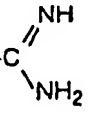
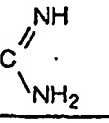
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
37		-H		1	C	Single bond
38		-H		1	C	Single bond
39		-H		1	C	Single bond
40		-H		1	C	Single bond
41	$-CH_3$	-H		1	C	Single bond
42	$-CH_2CH_3$	-H		1	C	Single bond
43	$-(CH_2)_2CH_3$	-H		1	C	Single bond
44	$-CH(CH_3)_2$	-H		1	C	Single bond
45	$-(CH_2)_3CH_3$	-H		1	C	Single bond
46	$-C(CH_3)_3$	-H		1	C	Single bond

Table 1 (continued)

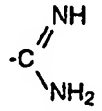
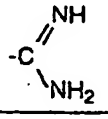
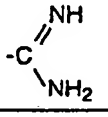
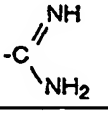
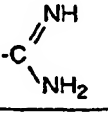
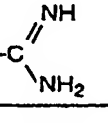
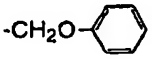
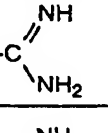
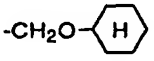
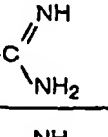
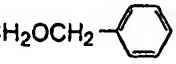
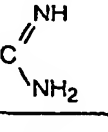
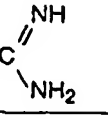
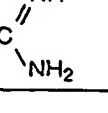
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert\\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
47	$-(CH_2)_4CH_3$	-H		1	C	Single bond
48	$-CH_2CH_2C(CH_3)_3$	-H		1	C	Single bond
49	$-(CH_2)_9CH_3$	-H		1	C	Single bond
50	$-CH_2Si(CH_3)_3$	-H		1	C	Single bond
51	$-CH_2CH_2Si(CH_3)_3$	-H		1	C	Single bond
52	$-CH_2OCH_3$	-H		1	C	Single bond
53		-H		1	C	Single bond
54		-H		1	C	Single bond
55		-H		1	C	Single bond
56	$-CH_2OH$	-H		1	C	Single bond
57	$-CH_2SCH_3$	-H		1	C	Single bond

Table 1 (continued)

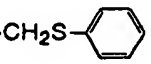
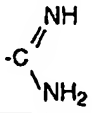
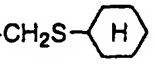
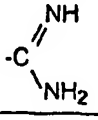
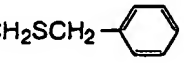
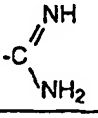
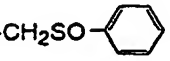
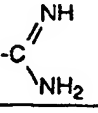
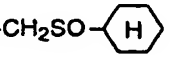
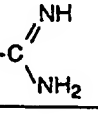
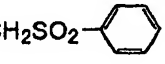
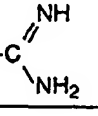
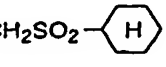
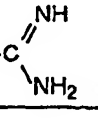
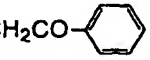
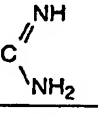
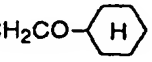
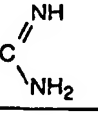
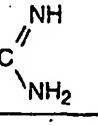
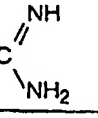
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
58		-H		1	C	Single bond
59		-H		1	C	Single bond
60		-H		1	C	Single bond
61		-H		1	C	Single bond
62		-H		1	C	Single bond
63		-H		1	C	Single bond
64		-H		1	C	Single bond
65		-H		1	C	Single bond
66		-H		1	C	Single bond
67	$-CH_2COOH$	-H		1	C	Single bond
68	$-CH_2COOCH_3$	-H		1	C	Single bond

Table 1 (continued)

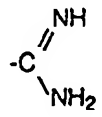
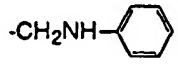
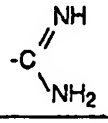
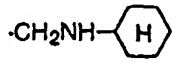
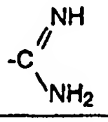
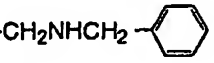
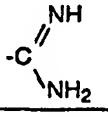
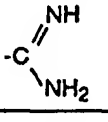
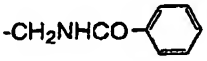
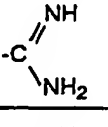
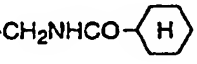
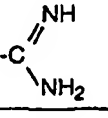
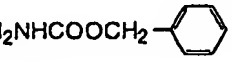
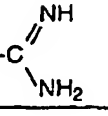
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
69	$-CH_2NHCH_3$	-H		1	C	Single bond
70		-H		1	C	Single bond
71		-H		1	C	Single bond
72		-H		1	C	Single bond
73	$-CH_2NHCOOCH_3$	-H		1	C	Single bond
74		-H		1	C	Single bond
75		-H		1	C	Single bond
76		-H		1	C	Single bond

Table 1 (continued)

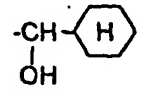
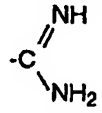
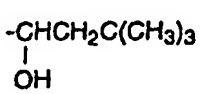
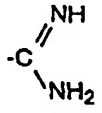
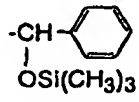
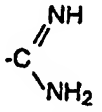
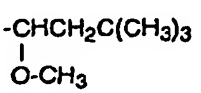
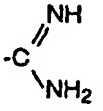
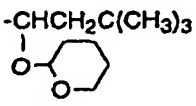
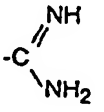
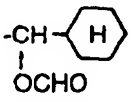
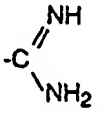
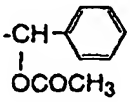
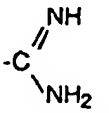
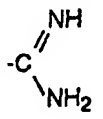
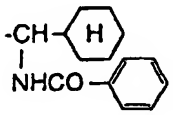
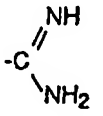
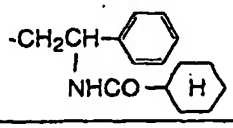
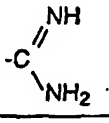
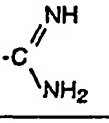
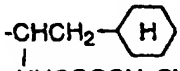
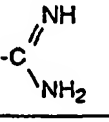
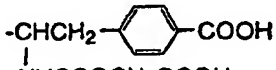
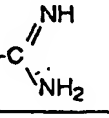
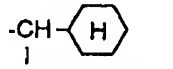
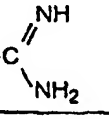
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
82		-H		1	C	Single bond
83		-H		1	C	Single bond
84		-H		1	C	Single bond
85		-H		1	C	Single bond
86		-H		1	C	Single bond
87		-H		1	C	Single bond
88		-H		1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
89	$-CHCH_2C(CH_3)_3$ $OCOOCH_3$	-H	$-C(=NH)-NH_2$	1	C	Single bond
90	$-CH(C_6H_5)$ $OCONH_2$	-H	$-C(=NH)-NH_2$	1	C	Single bond
91	$-CH(C_6H_5)$ $OCONHCH_3$	-H	$-C(=NH)-NH_2$	1	C	Single bond
92	$-CHCH_2C(CH_3)_3$ $OCON(CH_3)_2$	-H	$-C(=NH)-NH_2$	1	C	Single bond
93	$-CH_2CH(C_6H_5)$ $OCONHCH_2CH=CH_2$	-H	$-C(=NH)-NH_2$	1	C	Single bond
94	$-CHCH_2(C_6H_5)$ $NHCHO$	-H	$-C(=NH)-NH_2$	1	C	Single bond
95	$-CHCH_2C(CH_3)_3$ $NHCOCH_3$	-H	$-C(=NH)-NH_2$	1	C	Single bond
96	$-CHCH_2(C_6H_5)$ $NHCOCF_3$	-H	$-C(=NH)-NH_2$	1	C	Single bond
97	$-CHCH_2(C_6H_5)$ $NHCOOCH_3$	-H	$-C(=NH)-NH_2$	1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
98	$-CHC(SCH_3)(CH_3)_2$ $NHCOOC_2H_5$	-H		1	C	Single bond
99		-H		1	C	Single bond
100		-H		1	C	Single bond
101	$-CHCH_2C(CH_3)_3$ $NHCOOCH_2$ 	-H		1	C	Single bond
102	 $NHCOOCH_2CH=CH_2$	-H		1	C	Single bond
103	 $NHCOOCH_2COOH$	-H		1	C	Single bond
105 (Reference)	 $NHSO_2CH_3$	-H		1	C	Single bond

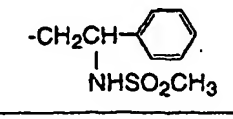
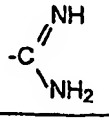
111	 $NHSO_2CH_3$	-H		1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
164	$-CH_2CH(CH_2)_3CH_3$ $NHSO_2CF_3$	-H	$-C(=NH)-NH_2$	1	C	Single bond
173	$-CHCH_2-C_6H_5$ NH_2	-H	$-C(=NH)-NH_2$	1	C	Single bond
174	$-CHCH_2-C_6H_5$ NH_2	-H	$-C(=NH)-NH_2$	1	C	Single bond
175	$-CHCH_2-C_6H_4(COOCH_3)$ NH_2	-H	$-C(=NH)-NH_2$	1	C	Single bond
176	$-CHCH_2-C_6H_4-CH_2COOH$ NH_2	-H	$-C(=NH)-NH_2$	1	C	Single bond
177	$-CHCH_2-C_6H_4(COCH_3)$ NH_2	-H	$-C(=NH)-NH_2$	1	C	Single bond
178	$-CHCH_2-C_6H_4-COOH$ NH_2	-H	$-C(=NH)-NH_2$	1	C	Single bond

Table 1 (continued)

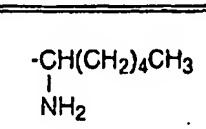
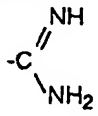
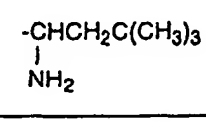
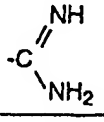
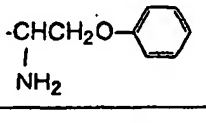
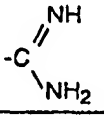
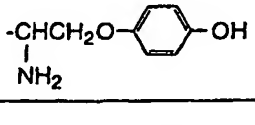
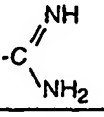
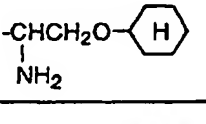
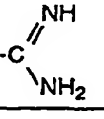
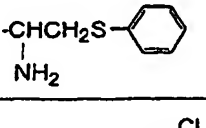
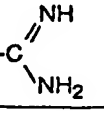
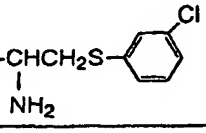
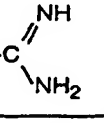
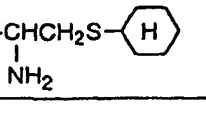
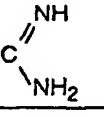
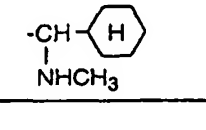
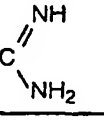
Compound No.	$-R^1\left(\begin{array}{c}-D-(CH)_m-E-R^4\\ \\ R^5\end{array}\right)$	$-R^2$	$-R^3$	n	A	Broken line
179		-H		1	C	Single bond
180		-H		1	C	Single bond
181		-H		1	C	Single bond
182		-H		1	C	Single bond
183		-H		1	C	Single bond
184		-H		1	C	Single bond
185		-H		1	C	Single bond
186		-H		1	C	Single bond
187		-H		1	C	Single bond

Table 1 (continued)

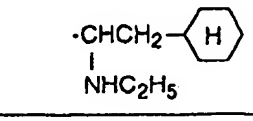
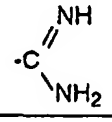
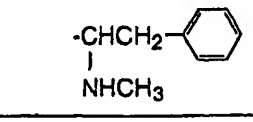
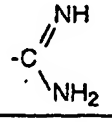
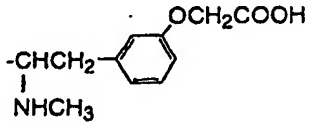
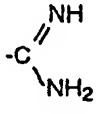
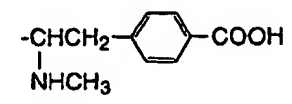
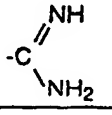
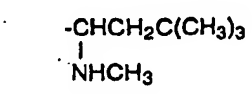
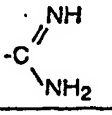
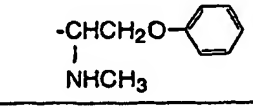
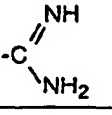
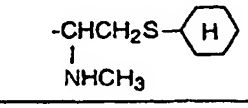
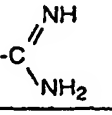
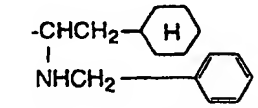
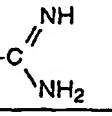
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
188		-H		1	C	Single bond
189		-H		1	C	Single bond
190		-H		1	C	Single bond
191		-H		1	C	Single bond
192		-H		1	C	Single bond
193		-H		1	C	Single bond
194		-H		1	C	Single bond
195		-H		1	C	Single bond

Table 1 (continued)

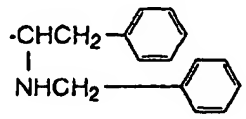
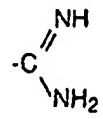
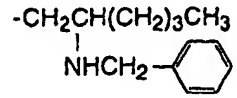
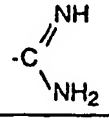
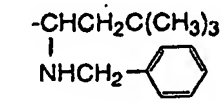
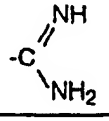
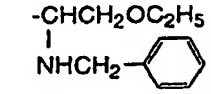
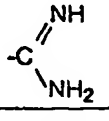
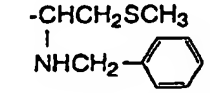
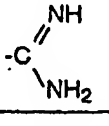
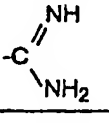
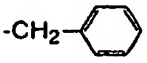
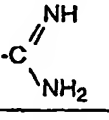
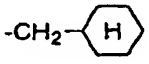
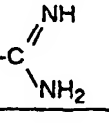
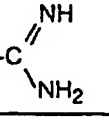
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
196		-H		1	C	Single bond
197		-H		1	C	Single bond
198		-H		1	C	Single bond
199		-H		1	C	Single bond
200		-H		1	C	Single bond
201		-H		1	C	——
202		-H		1	C	——
203		-H		1	C	——
204	$-(CH_2)_2CH_3$	-H		1	C	——

Table 1 (continued)

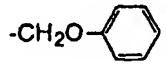
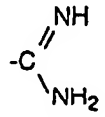
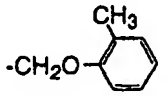
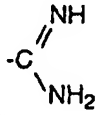
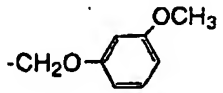
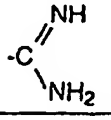
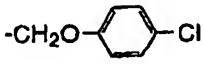
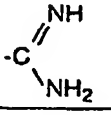
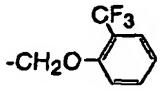
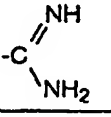
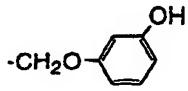
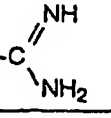
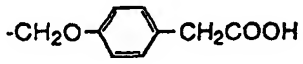
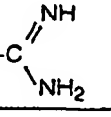
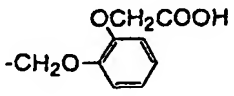
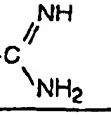
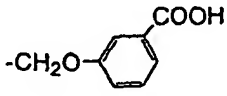
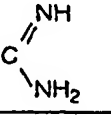
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	-R2	-R3	n	A	Broken line
205		-H		1	C	——
206		-H		1	C	——
207		-H		1	C	——
208		-H		1	C	——
209		-H		1	C	——
210		-H		1	C	——
211		-H		1	C	——
212		-H		1	C	——
213		-H		1	C	——

Table 1 (continued)

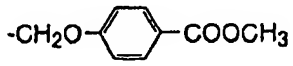
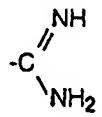
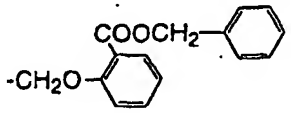
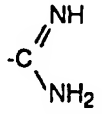
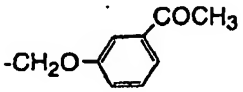
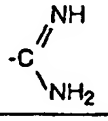
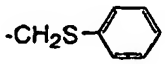
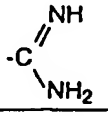
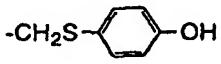
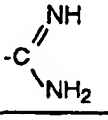
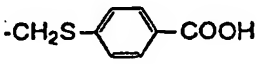
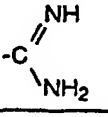
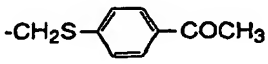
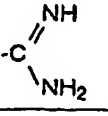
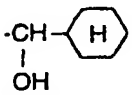
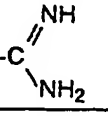
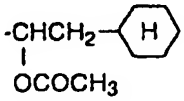
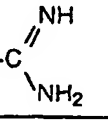
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	-R2	-R3	n	A	Broken line
214		-H		1	C	——
215		-H		1	C	——
216		-H		1	C	——
217		-H		1	C	——
218		-H		1	C	——
219		-H		1	C	——
220		-H		1	C	——
221		-H		1	C	——
222		-H		1	C	——

Table 1 (continued)

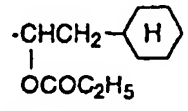
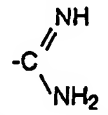
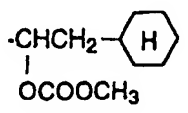
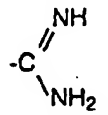
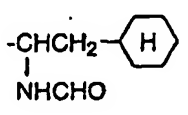
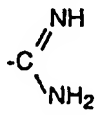
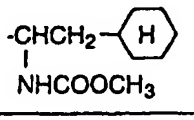
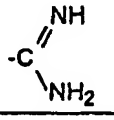
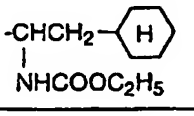
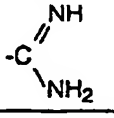
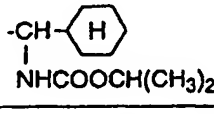
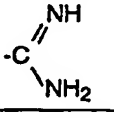
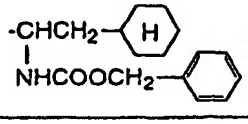
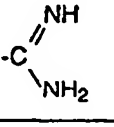
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
223		-H		1	C	——
224		-H		1	C	——
225		-H		1	C	——
226		-H		1	C	——
227		-H		1	C	——
228		-H		1	C	——
229		-H		1	C	——

Table 1 (continued)

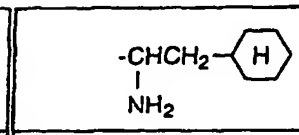
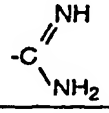
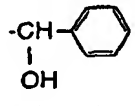
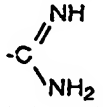
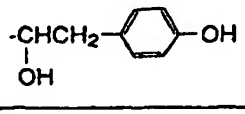
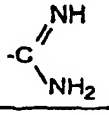
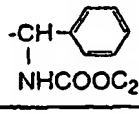
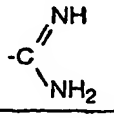
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
234		-H		1	C	——
235		-H		1	C	——
236		-H		1	C	——
238		-H		1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
240	$-CHCH_2OC(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NH)NH_2$	1	C	——
242	$-CHCH(CH_3)_2$ $NHCOOC_2H_5$	-H	$-C(=NH)NH_2$	1	C	——
244	$-CHC(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NH)NH_2$	1	C	——

Table 1 (continued)

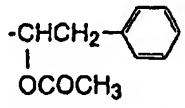
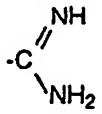
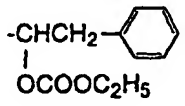
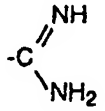
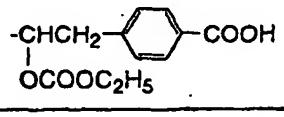
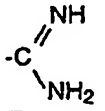
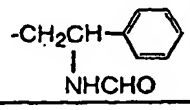
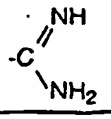
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
247		-H		1	C	——
248		-H		1	C	——
249		-H		1	C	——
254		-H		1	C	——

Table 1 (continued)

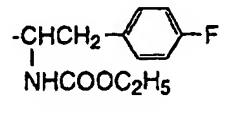
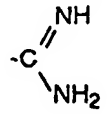
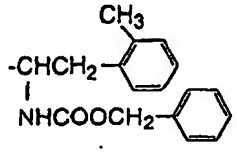
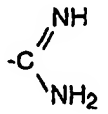
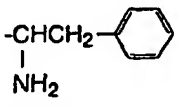
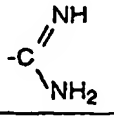
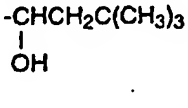
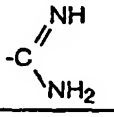
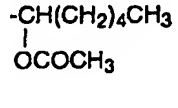
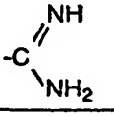
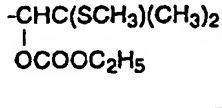
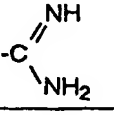
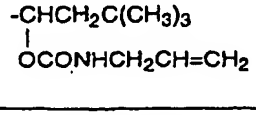
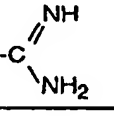
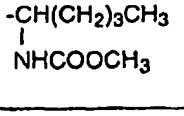
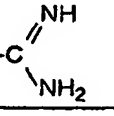
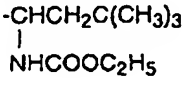
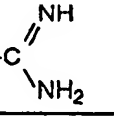
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	-R2	-R3	n	A	Broken line
255		-H		1	C	——
256		-H		1	C	——
257		-H		1	C	——
258		-H		1	C	——
259		-H		1	C	——
260		-H		1	C	——
261		-H		1	C	——
262		-H		1	C	——
263		-H		1	C	——

Table 1 (continued)

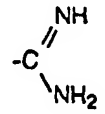
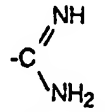
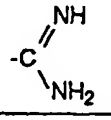
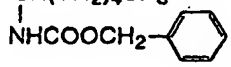
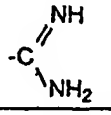
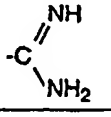
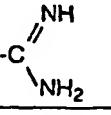
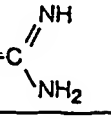
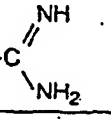
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
264	$-CHCH_2CH(C_2H_5)_2$ $NHCOOC_2H_5$	-H		1	C	——
265	$-CHCH_2C(CH_3)_3$ $NHCOOCH(CH_3)_2$	-H		1	C	——
266	$-CHCH_2C(CH_3)_3$ $NHCOOC(CH_3)_3$	-H		1	C	——
267	$-CH(CH_2)_4CH_3$ $NHCOOCH_2$ 	-H		1	C	——
268	$-CH_2CH(CH_2)_2CH_3$ $NHSO_2CH_3$	-H		1	C	——
271	$-CH_2CH(CH_2)_2CH_3$ NH_2	-H		1	C	——
272	$-(CH_2)_2$ 	-H		1	N	——
273	$-CH_2OCH_2$ 	-H		1	N	——

Table 1 (continued)

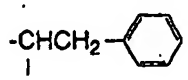
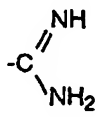
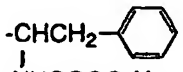
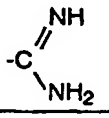
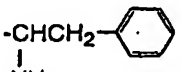
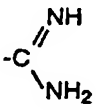
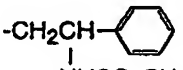
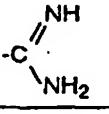
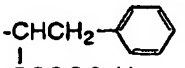
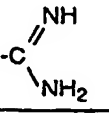
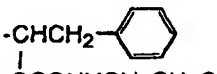
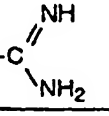
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
275		-H		1	N	——
277		-H		1	N	——
278		-H		1	N	——
279		-H		1	N	——
280		-H		1	N	——
281		-H		1	N	——

Table 1 (continued)

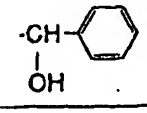
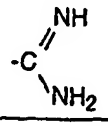
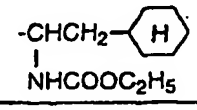
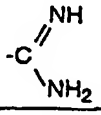
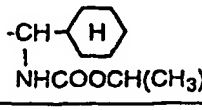
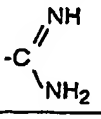
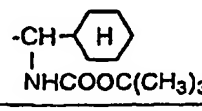
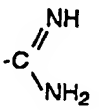
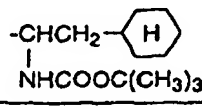
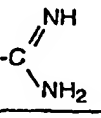
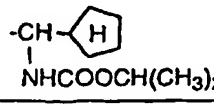
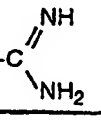
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	-R2	-R3	n	A	Broken line
282		-H		1	N	——
285		-H		1	N	——
286		-H		1	N	——
287		-H		1	N	——
288		-H		1	N	——
289		-H		1	N	——

Table 1 (continued)

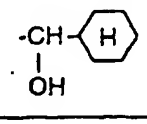
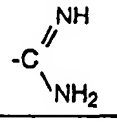
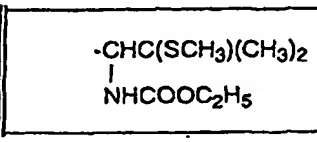
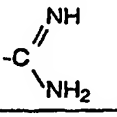
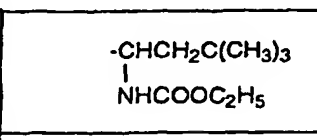
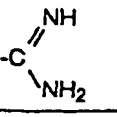
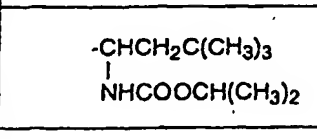
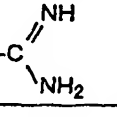
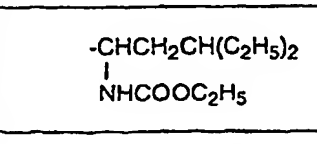
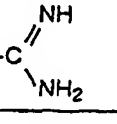
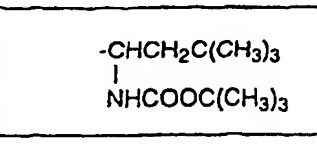
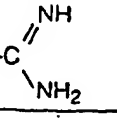
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	-R2	-R3	n	A	Broken line
290		-H		1	N	——
294		-H		1	N	——
296		-H		1	N	——
297		-H		1	N	——
298		-H		1	N	——
299		-H		1	N	——

Table 1 (continued)

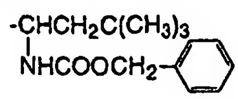
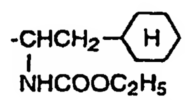
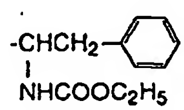
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
300		-H	$-C(=NH)NH_2$	1	N	——
301	$-CHCH_2C(CH_3)_3$ (with $-OH$ on the CH)	-H	$-C(=NH)NH_2$	1	N	——
306		-H	$-C(=NH)NH_2$	2	C	Single bond
307	$-CHCH_2C(CH_3)_3$ (with $-NHCOOC_2H_5$ on the CH)	-H	$-C(=NH)NH_2$	2	C	Single bond
308		-H	$-C(=NH)NH_2$	2	C	Single bond

Table 1 (continued)

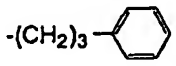
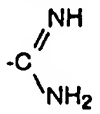
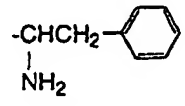
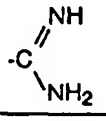
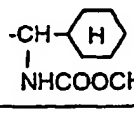
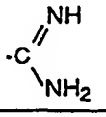
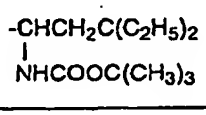
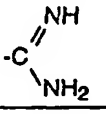
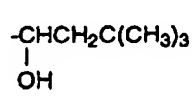
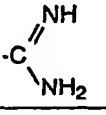
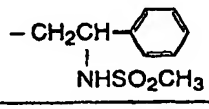
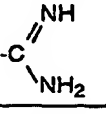
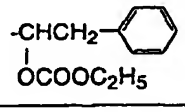
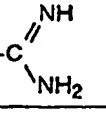
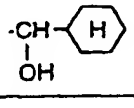
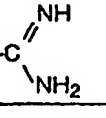
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
309		-H		2	C	Single bond
310		-H		2	C	Single bond
311		-H		2	C	Single bond
312		-H		2	C	Single bond
313		-H		2	C	Single bond
314		-H		2	C	Single bond
315		-H		2	C	Single bond
316		-H		2	C	Single bond

Table 1 (continued)

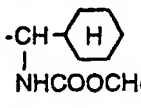
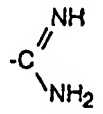
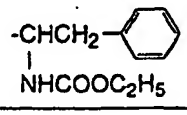
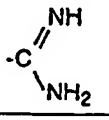
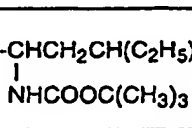
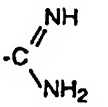
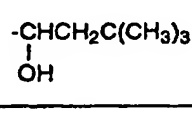
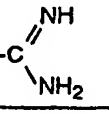
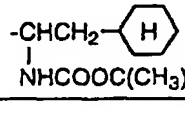
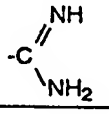
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
318		-H		2	C	——
320		-H		2	C	——
322		-H		2	C	——
323		-H		2	C	——
325		-H		2	N	——

Table 1 (continued)

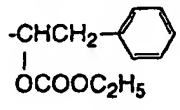
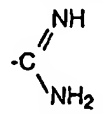
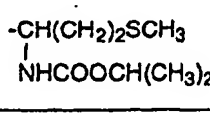
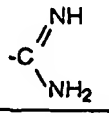
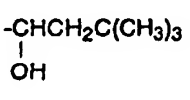
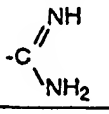
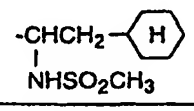
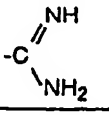
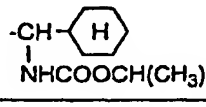
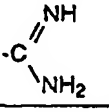
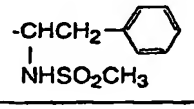
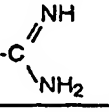
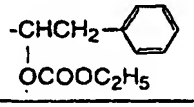
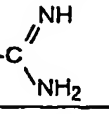
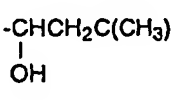
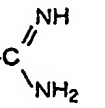
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
327		-H		2	N	——
329		-H		2	N	——
330		-H		2	N	——
331		$-CH_3$		1	C	Single bond
332		$-CH_3$		1	C	Single bond
333		$-CH_3$		1	C	Single bond
334		$-CH_3$		1	C	Single bond
335		$-CH_3$		1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
336	$-CHCH_2CH(C_2H_5)_2$ $NHCOOC(CH_3)_3$	$-CH_3$	$-C(=NH)-NH_2$	1	C	Single bond
337	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	$-CH_3$	$-C(=NH)-NH_2$	1	C	Single bond
338	$-CHCH_2-C_6H_5$ $NHSO_2CH_3$	$-CH_3$	$-C(=NH)-NH_2$	1	C	——
339	$-CH-C_6H_5$ $NHCOOCH(CH_3)_2$	$-CH_3$	$-C(=NH)-NH_2$	1	C	——
340	$-CHCH_2-C_6H_5$ $NHSO_2CH_3$	$-CH_3$	$-C(=NH)-NH_2$	1	C	——
341	$-CH_2CH-C_6H_5$ $OCOOC_2H_5$	$-CH_3$	$-C(=NH)-NH_2$	1	C	——
342	$-CHCH_2CH(C_2H_5)_2$ $NHCOOC(CH_3)_3$	$-CH_3$	$-C(=NH)-NH_2$	1	C	——
343	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	$-CH_3$	$-C(=NH)-NH_2$	1	C	——
344	$-CHCH_2C(CH_3)_3$ OH	$-CH_3$	$-C(=NH)-NH_2$	1	C	——

Table 1 (continued)

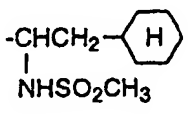
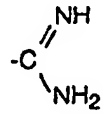
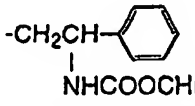
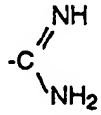
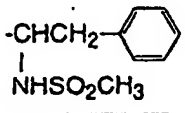
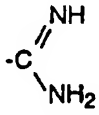
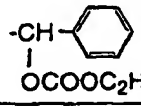
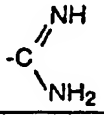
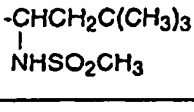
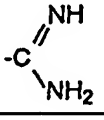
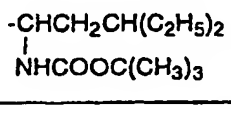
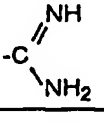
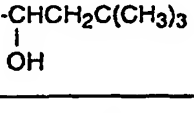
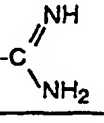
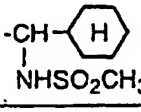
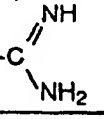
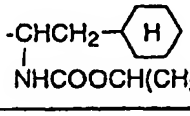
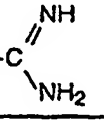
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
345		$-CH_3$		1	N	——
346		$-CH_3$		1	N	——
347		$-CH_3$		1	N	——
348		$-CH_3$		1	N	——
349		$-CH_3$		1	N	——
350		$-CH_3$		1	N	——
351		$-CH_3$		1	N	——
352		$-CH_3$		2	C	Single bond
353		$-CH_3$		2	C	Single bond

Table 1 (continued)

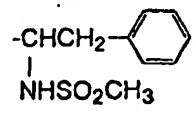
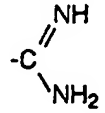
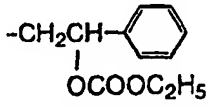
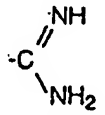
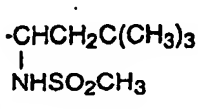
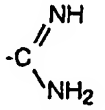
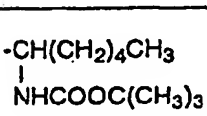
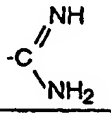
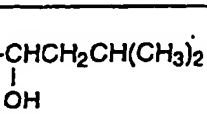
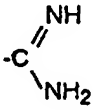
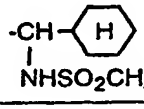
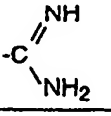
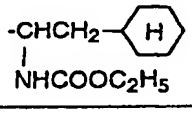
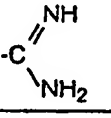
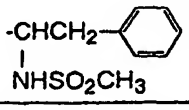
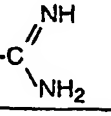
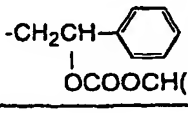
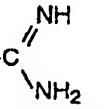
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4\right)$ with R^5	$-R^2$	$-R^3$	n	A	Broken line
354		$-CH_3$		2	C	Single bond
355		$-CH_3$		2	C	Single bond
356		$-CH_3$		2	C	Single bond
357		$-CH_3$		2	C	Single bond
358		$-CH_3$		2	C	Single bond
359		$-CH_3$		2	C	——
360		$-CH_3$		2	C	——
361		$-CH_3$		2	C	——
362		$-CH_3$		2	C	——

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
363	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	$-CH_3$	$-C(=NH)-NH_2$	2	C	——
364	$-CHC(SCH_3)(CH_3)_2$ $NHCOOC(CH_3)_3$	$-CH_3$	$-C(=NH)-NH_2$	2	C	——
365	$-CHCH_2CH(CH_3)_3$ NH_2	$-CH_3$	$-C(=NH)-NH_2$	2	C	——
366	$-CHCH_2-C_6H_5$(H) $NHCOOC_2H_5$	$-CH_3$	$-C(=NH)-NH_2$	2	N	——
367	$-CHCH_2-C_6H_5$(H) $NHSO_2CH_3$	$-CH_3$	$-C(=NH)-NH_2$	2	N	——
368	$-CH-C_6H_5$ $NHSO_2CH_3$	$-CH_3$	$-C(=NH)-NH_2$	2	N	——
369	$-CHCH_2-C_6H_4-COOH$ $OCOOCH(CH_3)_2$	$-CH_3$	$-C(=NH)-NH_2$	2	N	——
370	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_2COOH$	$-CH_3$	$-C(=NH)-NH_2$	2	N	——
371	$-CH(CH_2)_2SCH_3$ $NHCOOC(CH_3)_3$	$-CH_3$	$-C(=NH)-NH_2$	2	N	——
372	$-CH_2CH(CH_2)_3CH_3$ OH	$-CH_3$	$-C(=NH)-NH_2$	2	N	——

Table 1 (continued)

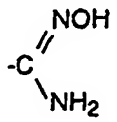
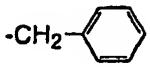
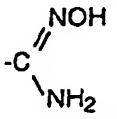
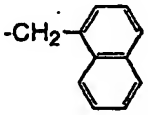
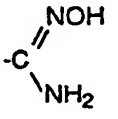
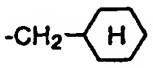
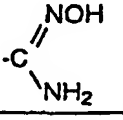
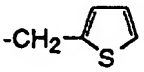
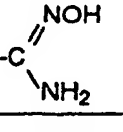
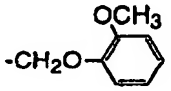
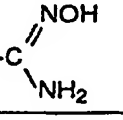
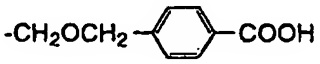
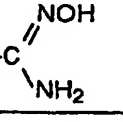
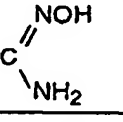
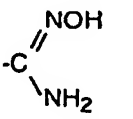
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4, R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
373		-H		1	C	Single bond
374		-H		1	C	Single bond
375		-H		1	C	Single bond
376		-H		1	C	Single bond
377		-H		1	C	Single bond
378		-H		1	C	Single bond
379		-H		1	C	Single bond
380	$-CH_2SC_2H_5$	-H		1	C	Single bond
381	$-(CH_2)_4COOH$	-H		1	C	Single bond

Table 1 (continued)

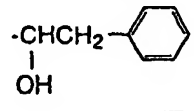
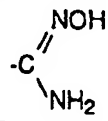
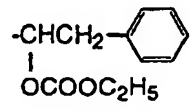
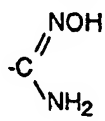
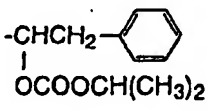
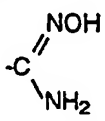
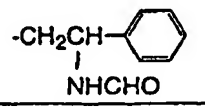
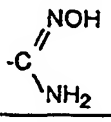
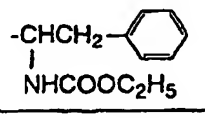
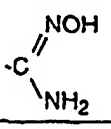
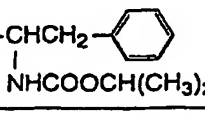
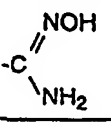
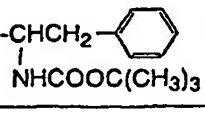
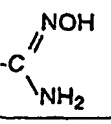
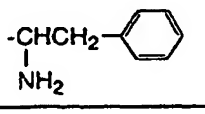
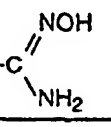
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
383		-H		1	C	Single bond
384		-H		1	C	Single bond
385		-H		1	C	Single bond
386		-H		1	C	Single bond
387		-H		1	C	Single bond
388		-H		1	C	Single bond
389		-H		1	C	Single bond
390		-H		1	C	Single bond

Table 1 (continued)

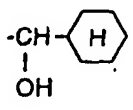
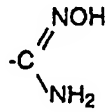
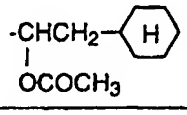
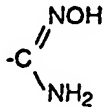
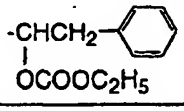
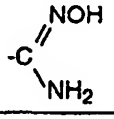
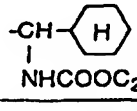
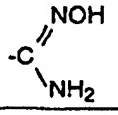
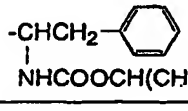
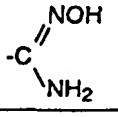
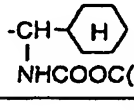
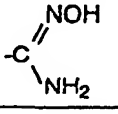
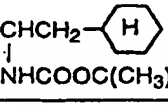
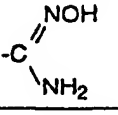
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
391		-H		1	C	Single bond
392		-H		1	C	Single bond
393		-H		1	C	Single bond
394		-H		1	C	Single bond
395		-H		1	C	Single bond
396		-H		1	C	Single bond
397		-H		1	C	Single bond

Table 1 (continued)

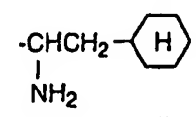
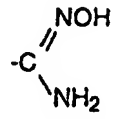
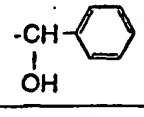
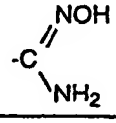
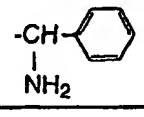
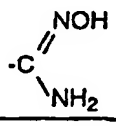
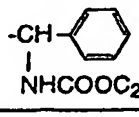
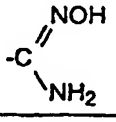
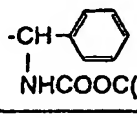
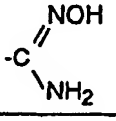
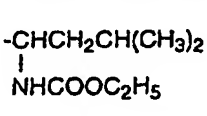
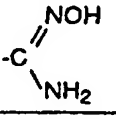
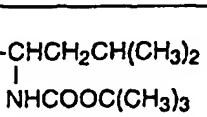
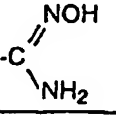
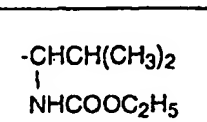
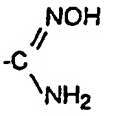
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
400		-H		1	C	Single bond
401		-H		1	C	Single bond
402		-H		1	C	Single bond
403		-H		1	C	Single bond
404		-H		1	C	Single bond
405		-H		1	C	Single bond
406		-H		1	C	Single bond
407		-H		1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
408	$-CHCH(CH_3)_2$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)-NH_2$	1	C	Single bond
409	$-CHC(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	Single bond
410	$-CHC(CH_3)_3$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)-NH_2$	1	C	Single bond
411	$-CH(CH_2)_4CH_3$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	Single bond
412	$-CH(CH_2)_4CH_3$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)-NH_2$	1	C	Single bond
413	$-CHCH_2CH_2SCH_3$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	Single bond
414	$-CHCH_2CH_2SCH_3$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)-NH_2$	1	C	Single bond
415	$-CH(CH_2)_4CH_3$ $OCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	Single bond
416	$-CHCH_2C(CH_3)_3$ $OCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	Single bond
417	$-CHCH_2CH(C_2H_5)_2$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	Single bond
418	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	Single bond

Table 1 (continued)

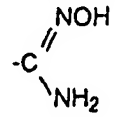
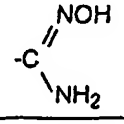
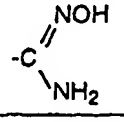
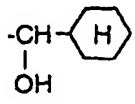
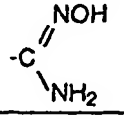
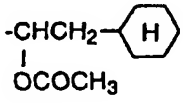
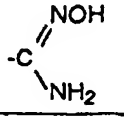
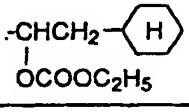
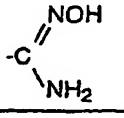
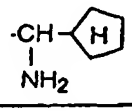
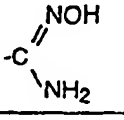
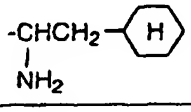
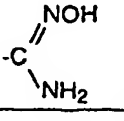
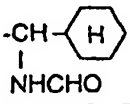
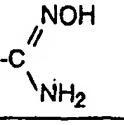
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
419	$-CHC(SCH_3)(CH_3)_2$ $NHCOOC_2H_5$	-H		1	C	Single bond
420	$-CHCH_2C(CH_3)_3$ $NHCOOCH(CH_3)_2$	-H		1	C	Single bond
421	$-CHCH_2C(CH_3)_3$ NH_2	-H		1	C	Single bond
422		-H		1	C	——
423		-H		1	C	——
424		-H		1	C	——
425		-H		1	C	——
426		-H		1	C	——
427		-H		1	C	——

Table 1 (continued)

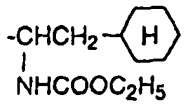
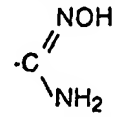
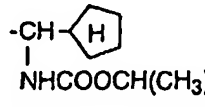
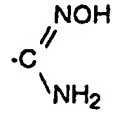
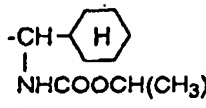
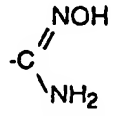
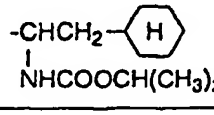
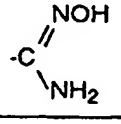
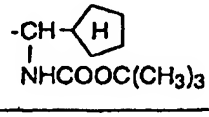
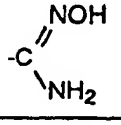
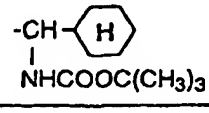
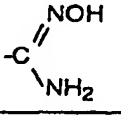
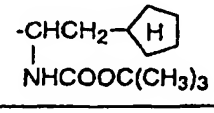
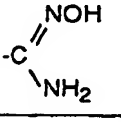
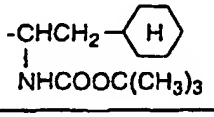
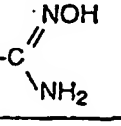
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
428		-H		1	C	——
429		-H		1	C	——
430		-H		1	C	——
431		-H		1	C	——
432		-H		1	C	——
433		-H		1	C	——
434		-H		1	C	——
435		-H		1	C	——

Table 1 (continued)

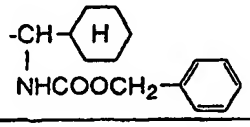
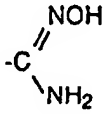
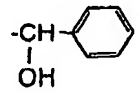
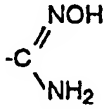
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
436		-H		1	C	——
443		-H		1	C	——

Table 1 (continued)

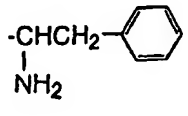
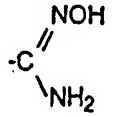
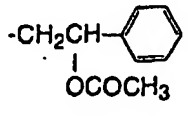
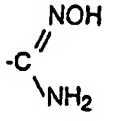
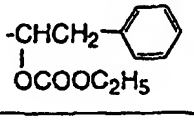
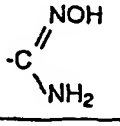
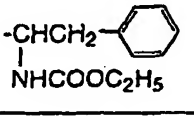
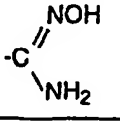
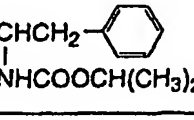
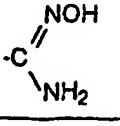
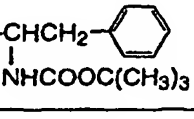
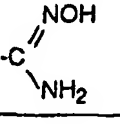
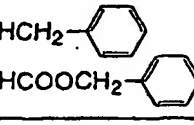
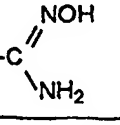
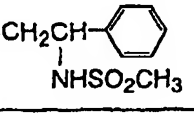
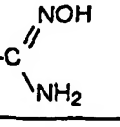
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
444		-H		1	C	——
445		-H		1	C	——
446		-H		1	C	——
447		-H		1	C	——
448		-H		1	C	——
449		-H		1	C	——
450		-H		1	C	——
451		-H		1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
453	$-CH(CH_2)_4CH_3$ OH	-H	$-C(=NOH)-NH_2$	1	C	——
454	$-CHCH_2C(CH_3)_3$ OH	H	$-C(=NOH)-NH_2$	1	C	——
455	$-CHCH_2CH(C_2H_5)_2$ $OCOCH_3$	-H	$-C(=NOH)-NH_2$	1	C	——
456	$-CHCH_2C(CH_3)_3$ $OCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——
457	$-CH_2CH(CH_2)_2CH_3$ NHCHO	H	$-C(=NOH)-NH_2$	1	C	——
458	$-CHCH_2C(CH_3)_3$ $NHCOOCH_3$	-H	$-C(=NOH)-NH_2$	1	C	——
459	$-CH(CH_2)_4CH_3$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——
460	$-CHCH_2CH(C_2H_5)_2$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——
461	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——

Table 1 (continued)

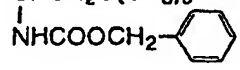
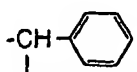
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
462	$-CH(CH_2)_4CH_3$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
463	$-CHCH_2CH(C_2H_5)_2$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
464	$-CHCH_2C(CH_3)_3$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
465	$-CH(CH_2)_4CH_3$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)-NH_2$	1	C	——
466	$-CHCH_2CH(C_2H_5)_2$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)-NH_2$	1	C	——
467	$-CHCH_2C(CH_3)_3$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)-NH_2$	1	C	——
468	$-CH(CH_2)_2SCH_3$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)-NH_2$	1	C	——
469	$-CHCH_2C(CH_3)_3$ $NHCOOCH_2$– 	-H	$-C(=NOH)-NH_2$	1	C	——
470	$-CHCH_2C(CH_3)_3$ NH_2	-H	$-C(=NOH)-NH_2$	1	C	——
471	$-CH$–  $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——

Table 1 (continued)

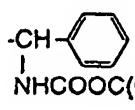
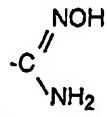
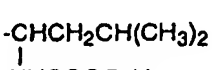
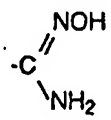
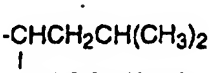
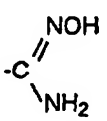
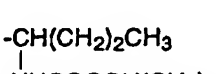
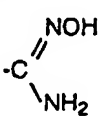
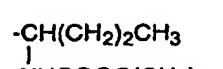
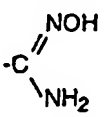
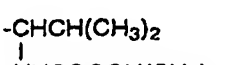
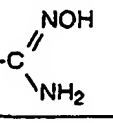
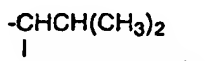
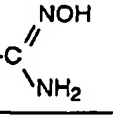
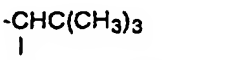
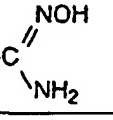
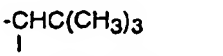
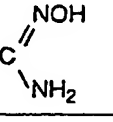
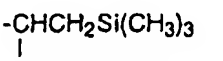
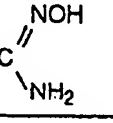
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
472		-H		1	C	——
473		-H		1	C	——
474		-H		1	C	——
475		H		1	C	——
476		-H		1	C	——
477		H		1	C	——
478		-H		1	C	——
479		-H		1	C	——
480		-H		1	C	——
481		-H		1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
482	$-CHCH_2Si(CH_3)_3$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
483	$-CHCH_2CH_2SCH_3$ $NHCOOC_2H_5$	H	$-C(=NOH)-NH_2$	1	C	——
484	$-CHCH_2CH_2SCH_3$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
485	$-CHCH_2OC(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——
486	$-CHCH_2OC(CH_3)_3$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
487	$-CHCH_2OC(CH_3)_2C_2H_5$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——
488	$-CHCH_2OC(CH_3)_2C_2H_5$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
489	$-CHCH_2OC(C_2H_5)_2CH_3$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——
490	$-CHCH_2OC(C_2H_5)_2CH_3$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
491	$-CHCH_2OC(CH_3)_2CH(CH_3)_2$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
492	$-CHCH_2SC(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
493	$-CHCH_2SC(CH_3)_2C_2H_5$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——
494	$-CHCH_2SC(CH_3)_2C_2H_5$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
495	$-CHC(CH_3)_2SC_2H_5$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——
496	$-CHC(CH_3)_2SC_2H_5$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
497	$-CHC(CH_3)_2SCH(CH_3)_2$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——
498	$-CHC(CH_3)_2SCH(CH_3)_2$ $NHCOOCH(CH_3)_2$	H	$-C(=NOH)-NH_2$	1	C	——
499	$-CHC(CH_3)_2SCH(C_2H_5)_2$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——
500	$-CHC(CH_3)_2SCH(C_2H_5)_2$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——

Table 1 (continued)

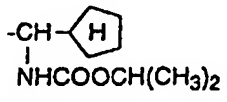
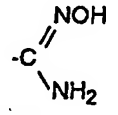
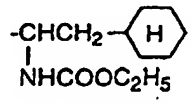
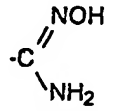
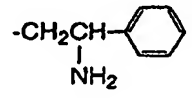
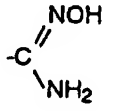
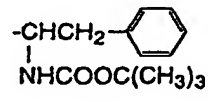
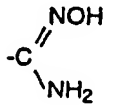
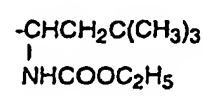
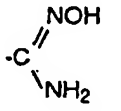
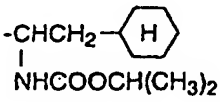
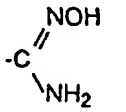
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
505		-H		1	N	——
506		H		1	N	——
507		-H		1	N	——
508		-H		1	N	——
509		-H		1	N	——
511		$-CH_3$		2	C	Single bond

Table 1 (continued)

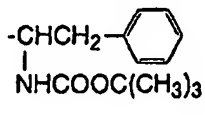
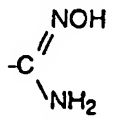
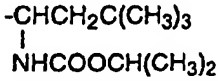
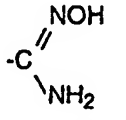
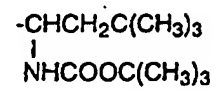
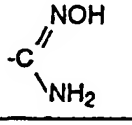
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
512		$-CH_3$		2	C	Single bond
513		$-CH_3$		2	C	Single bond
514		$-CH_3$		2	C	Single bond

Table 1 (continued)

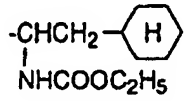
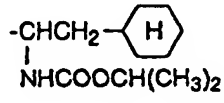
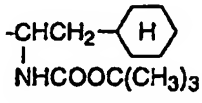
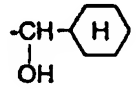
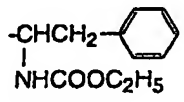
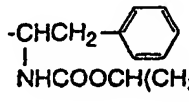
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
747		-H	$-NH_2$	1	C	Single bond
748		-H	$-NH_2$	1	C	Single bond
749		-H	$-NH_2$	1	C	Single bond
750		-H	$-NH_2$	1	C	Single bond
752		-H	$-NH_2$	1	C	Single bond
753		-H	$-NH_2$	1	C	Single bond

Table 1 (continued)

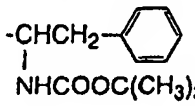
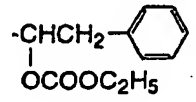
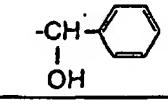
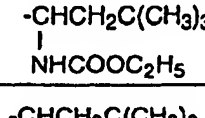
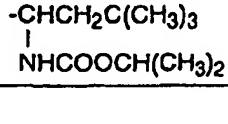
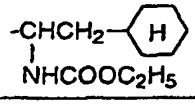
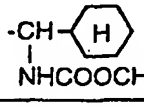
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
754		-H	$-NH_2$	1	C	Single bond
755		-H	$-NH_2$	1	C	Single bond
756		-H	$-NH_2$	1	C	Single bond
757		-H	$-NH_2$	1	C	Single bond
758		-H	$-NH_2$	1	C	Single bond
761		-H	$-NH_2$	1	C	——
762		-H	$-NH_2$	1	C	——

Table 1 (continued)

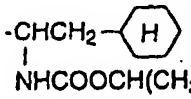
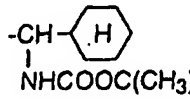
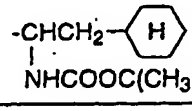
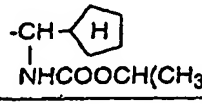
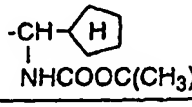
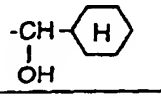
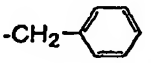
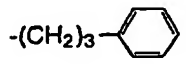
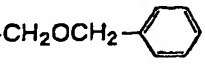
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
763		-H	$-NH_2$	1	C	——
764		-H	$-NH_2$	1	C	——
765		-H	$-NH_2$	1	C	——
766		-H	$-NH_2$	1	C	——
767		-H	$-NH_2$	1	C	——
768		-H	$-NH_2$	1	C	——
769		-H	$-NH_2$	1	C	——
770		-H	$-NH_2$	1	C	——
771		-H	$-NH_2$	1	C	——

Table 1 (continued)

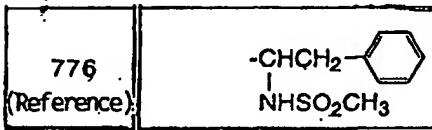
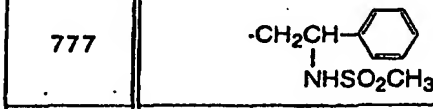
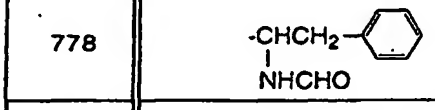
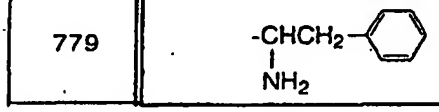
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
776 (Reference)		-H	$-NH_2$	1	C	——
777		-H	$-NH_2$	1	C	——
778		-H	$-NH_2$	1	C	——
779		-H	$-NH_2$	1	C	——

Table 1 (continued)

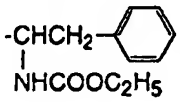
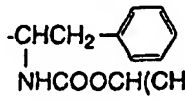
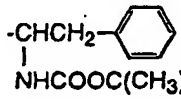
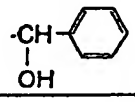
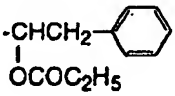
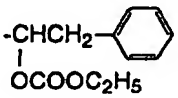
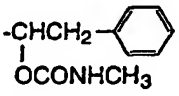
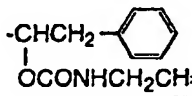
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
780		-H	$-NH_2$	1	C	——
781		-H	$-NH_2$	1	C	——
782		-H	$-NH_2$	1	C	——
783		-H	$-NH_2$	1	C	——
784		-H	$-NH_2$	1	C	——
785		-H	$-NH_2$	1	C	——
786		-H	$-NH_2$	1	C	——
787		-H	$-NH_2$	1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
793	$-CHC(SCH_3)(CH_3)_2$ $\vert$ $NHCOOC_2H_5$	-H	$-NH_2$	1	C	——
794	$-CHCH_2C(CH_3)_3$ $\vert$ $NHCOOC_2H_5$	-H	$-NH_2$	1	C	——
795	$-CHCH_2CH(C_2H_5)_2$ $\vert$ $NHCOOC_2H_5$	-H	$-NH_2$	1	C	——
796	$-CH(CH_2)_4CH_3$ $\vert$ $NHCOOC_2H_5$	-H	$-NH_2$	1	C	——
797	$-CHCH_2C(CH_3)_3$ $\vert$ $NHCOOCH(CH_3)_2$	-H	$-NH_2$	1	C	——
798	$-CHCH_2CH(C_2H_5)_2$ $\vert$ $NHCOOCH(CH_3)_2$	-H	$-NH_2$	1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
799	$-CHCH_2C(CH_3)_3$ $\vert$ $NHCOOC(CH_3)_3$	-H	$-NH_2$	1	C	——
800	$-CHCH_2CH(C_2H_5)_2$ $\vert$ $NHCOOC(CH_3)_3$	-H	$-NH_2$	1	C	——
801	$-CH(CH_2)_2SCH_3$ $\vert$ $NHCOOC(CH_3)_3$	-H	$-NH_2$	1	C	——
802	$-CHCH_2C(CH_3)_3$ $\vert$ $NHCOOCH_2-$ 	-H	$-NH_2$	1	C	——
803	$-CHCH_2C(CH_3)_3$ $\vert$ OH	-H	$-NH_2$	1	C	——
804	$-CHCH_2C(CH_3)_3$ $\vert$ $OCOOC_2H_5$	-H	$-NH_2$	1	C	——

816	$-CHCH_2-$  $\vert$ $NHCOOC_2H_5$	-H	$-NH_2$	2	C	Single bond
817	$-CHCH_2-$  $\vert$ $NHCOOCH(CH_3)_2$	-H	$-NH_2$	2	C	Single bond

Table 1 (continued)

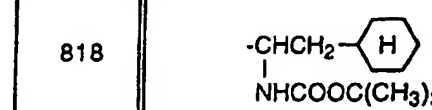
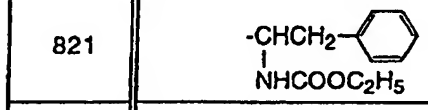
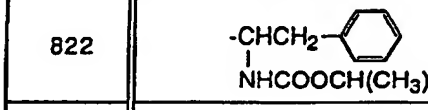
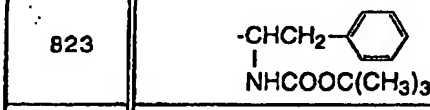
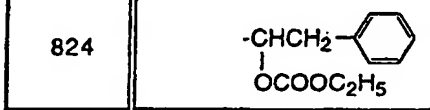
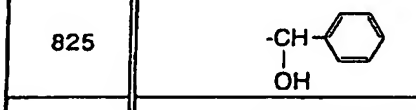
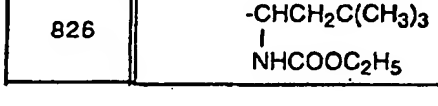
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
818		-H	$-NH_2$	2	C	Single bond
819		-H	$-NH_2$	2	C	Single bond
821		-H	$-NH_2$	2	C	Single bond
822		-H	$-NH_2$	2	C	Single bond
823		-H	$-NH_2$	2	C	Single bond
824		-H	$-NH_2$	2	C	Single bond
825		-H	$-NH_2$	2	C	Single bond
826		-H	$-NH_2$	2	C	Single bond

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
827	$-CHCH_2C(CH_3)_3$ $NHCOOCH(CH_3)_2$	-H	$-NH_2$	2	C	Single bond
830	$-CHCH_2$(H) $NHCOOC_2H_5$	-H	$-NH_2$	2	C	——
831	$-CHCH_2$(H) $NHCOOCH(CH_3)_2$	-H	$-NH_2$	2	C	——
832	$-CHCH_2$(H) $NHCOOC(CH_3)_3$	-H	$-NH_2$	2	C	——
833	$-CH$(H) OH	-H	$-NH_2$	2	C	——
835	$-CHCH_2$(C6H5) $NHCOOC_2H_5$	-H	$-NH_2$	2	C	——

Table 1 (continued)

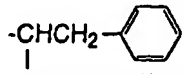
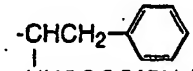
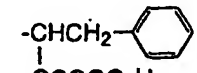
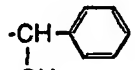
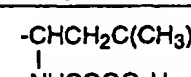
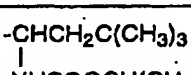
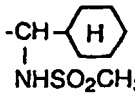
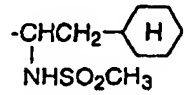
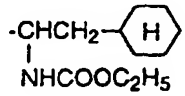
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
836		-H	$-NH_2$	2	C	——
837		-H	$-NH_2$	2	C	——
838		-H	$-NH_2$	2	C	——
839		-H	$-NH_2$	2	C	——
840		-H	$-NH_2$	2	C	——
841		-H	$-NH_2$	2	C	——
842		$-CH_3$	$-NH_2$	1	C	Single bond
843		$-CH_3$	$-NH_2$	1	C	Single bond
844		$-CH_3$	$-NH_2$	1	C	Single bond

Table 1 (continued)

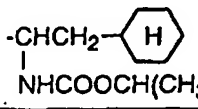
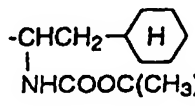
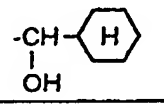
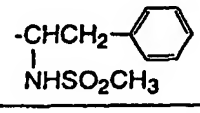
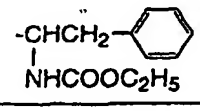
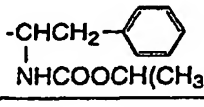
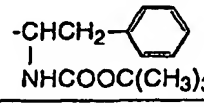
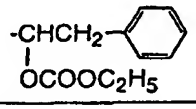
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
845		$-CH_3$	$-NH_2$	1	C	Single bond
846		$-CH_3$	$-NH_2$	1	C	Single bond
847		$-CH_3$	$-NH_2$	1	C	Single bond
848		$-CH_3$	$-NH_2$	1	C	Single bond
849		$-CH_3$	$-NH_2$	1	C	Single bond
850		$-CH_3$	$-NH_2$	1	C	Single bond
851		$-CH_3$	$-NH_2$	1	C	Single bond
852		$-CH_3$	$-NH_2$	1	C	Single bond

Table 1 (continued)

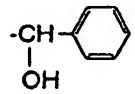
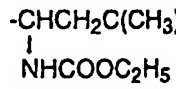
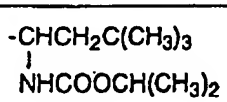
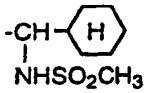
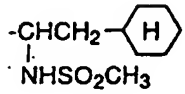
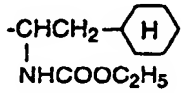
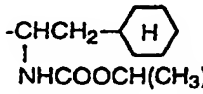
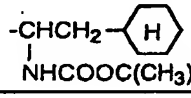
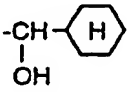
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
853		$-CH_3$	$-NH_2$	1	C	Single bond
854		$-CH_3$	$-NH_2$	1	C	Single bond
855		$-CH_3$	$-NH_2$	1	C	Single bond
856		$-CH_3$	$-NH_2$	1	C	——
857		$-CH_3$	$-NH_2$	1	C	——
858		$-CH_3$	$-NH_2$	1	C	——
859		$-CH_3$	$-NH_2$	1	C	——
860		$-CH_3$	$-NH_2$	1	C	——
861		$-CH_3$	$-NH_2$	1	C	——

Table 1 (continued)

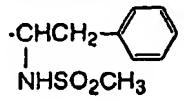
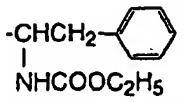
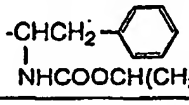
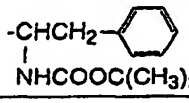
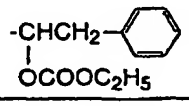
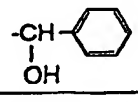
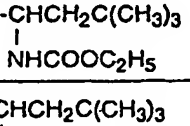
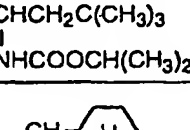
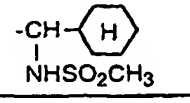
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
862		$-CH_3$	$-NH_2$	1	C	——
863		$-CH_3$	$-NH_2$	1	C	——
864		$-CH_3$	$-NH_2$	1	C	——
865		$-CH_3$	$-NH_2$	1	C	——
866		$-CH_3$	$-NH_2$	1	C	——
867		$-CH_3$	$-NH_2$	1	C	——
868		$-CH_3$	$-NH_2$	1	C	——
869		$-CH_3$	$-NH_2$	1	C	——
870		$-CH_3$	$-NH_2$	2	C	Single bond

Table 1 (continued)

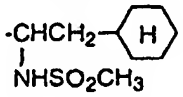
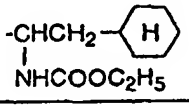
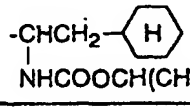
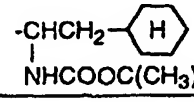
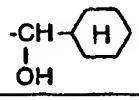
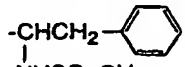
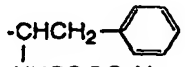
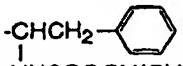
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
871		$-CH_3$	$-NH_2$	2	C	Single bond
872		$-CH_3$	$-NH_2$	2	C	Single bond
873		$-CH_3$	$-NH_2$	2	C	Single bond
874		$-CH_3$	$-NH_2$	2	C	Single bond
875		$-CH_3$	$-NH_2$	2	C	Single bond
876		$-CH_3$	$-NH_2$	2	C	Single bond
877		$-CH_3$	$-NH_2$	2	C	Single bond
878		$-CH_3$	$-NH_2$	2	C	Single bond

Table 1 (continued)

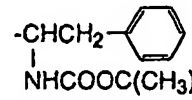
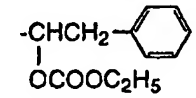
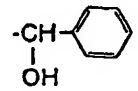
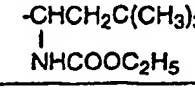
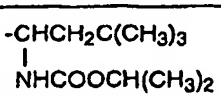
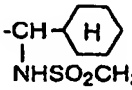
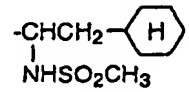
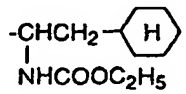
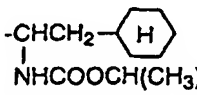
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
879		$-CH_3$	$-NH_2$	2	C	Single bond
880		$-CH_3$	$-NH_2$	2	C	Single bond
881		$-CH_3$	$-NH_2$	2	C	Single bond
882		$-CH_3$	$-NH_2$	2	C	Single bond
883		$-CH_3$	$-NH_2$	2	C	Single bond
884		$-CH_3$	$-NH_2$	2	C	——
885		$-CH_3$	$-NH_2$	2	C	——
886		$-CH_3$	$-NH_2$	2	C	——
887		$-CH_3$	$-NH_2$	2	C	——

Table 1 (continued)

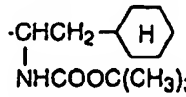
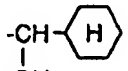
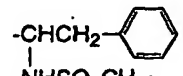
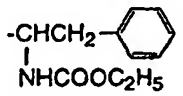
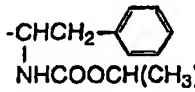
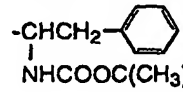
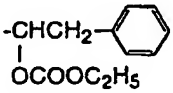
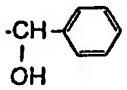
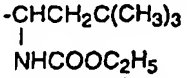
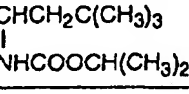
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
888		$-CH_3$	$-NH_2$	2	C	——
889		$-CH_3$	$-NH_2$	2	C	——
890		$-CH_3$	$-NH_2$	2	C	——
891		$-CH_3$	$-NH_2$	2	C	——
892		$-CH_3$	$-NH_2$	2	C	——
893		$-CH_3$	$-NH_2$	2	C	——
894		$-CH_3$	$-NH_2$	2	C	——
895		$-CH_3$	$-NH_2$	2	C	——
896		$-CH_3$	$-NH_2$	2	C	——
897		$-CH_3$	$-NH_2$	2	C	——

Table 1 (continued)

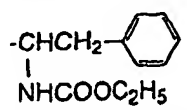
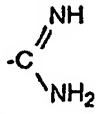
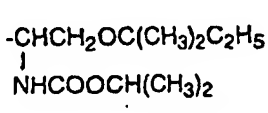
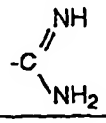
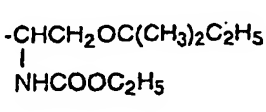
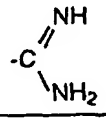
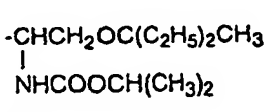
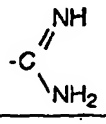
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
972		-H		1	C	Single bond
977		-H		1	C	——
978		-H		1	C	——
979		-H		1	C	——

Table 1 (continued)

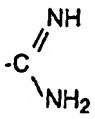
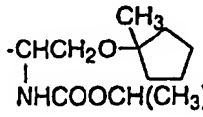
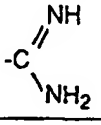
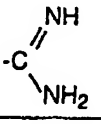
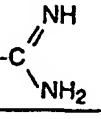
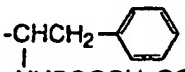
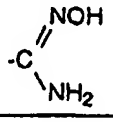
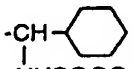
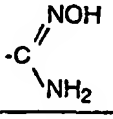
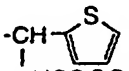
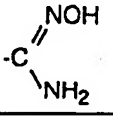
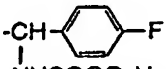
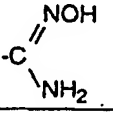
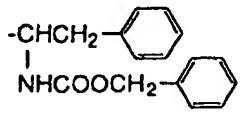
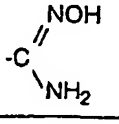
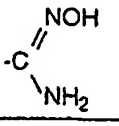
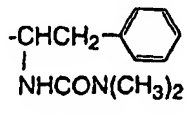
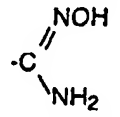
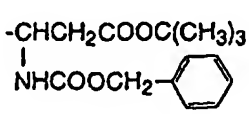
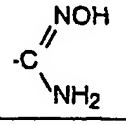
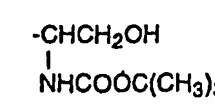
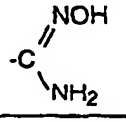
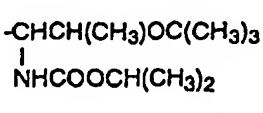
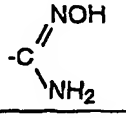
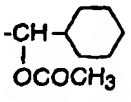
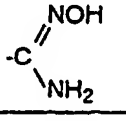
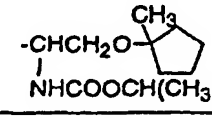
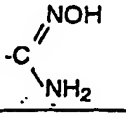
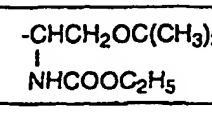
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
980	$-CHCH_2SC(CH_3)_3$ $NHCOOC_2H_5$	-H		1	C	——
981	 $NHCOOCH(CH_3)_2$	-H		1	C	——
982	$-CHCH(CH_3)OC(CH_3)_3$ $NHCOOCH(CH_3)_2$	-H		1	C	——
983	$-CHC(CH_3)_2SCH(CH_3)_2$ $NHCOOC_2H_5$	-H		1	C	——
984	 $NHCOOCH_2COOC_2H_5$	-H		1	C	Single bond
985	 $NHCOOC_2H_5$	-H		1	C	Single bond
986	 $NHCOOC_2H_5$	-H		1	C	Single bond
987	 $NHCOOC_2H_5$	-H		1	C	Single bond
988	 $NHCOOCH_2$	-H		1	C	Single bond
989	$-CHCH_2C(CH_3)_3$ $NHCOOC(CH_3)_3$	-H		1	C	Single bond

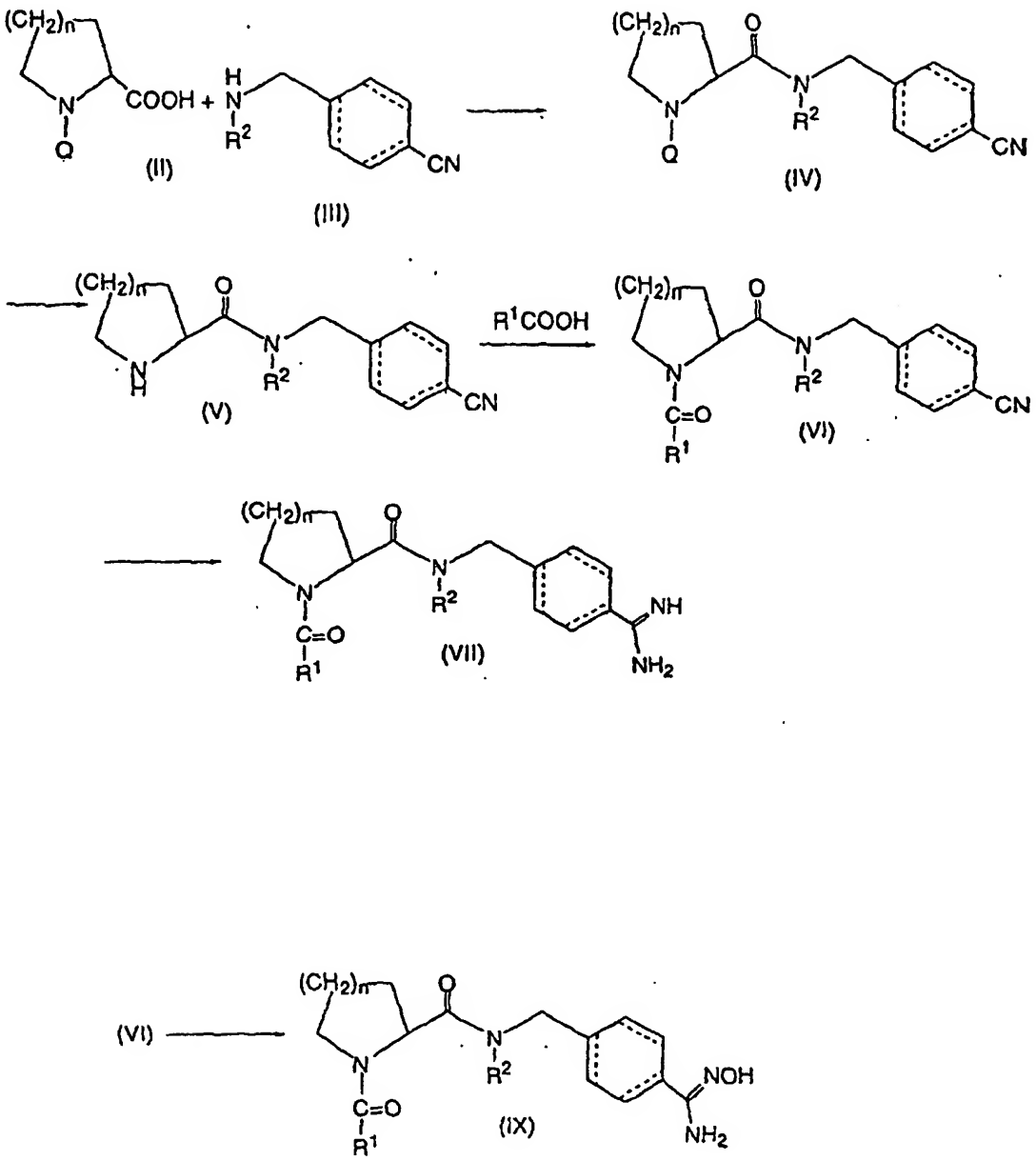
Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
990		-H		1	C	Single bond
991		-H		1	C	Single bond
992		-H		1	C	——
993		-H		1	C	——
994		-H		1	C	——
995		-H		1	C	——
1003		-H	$-NH_2$	1	C	——

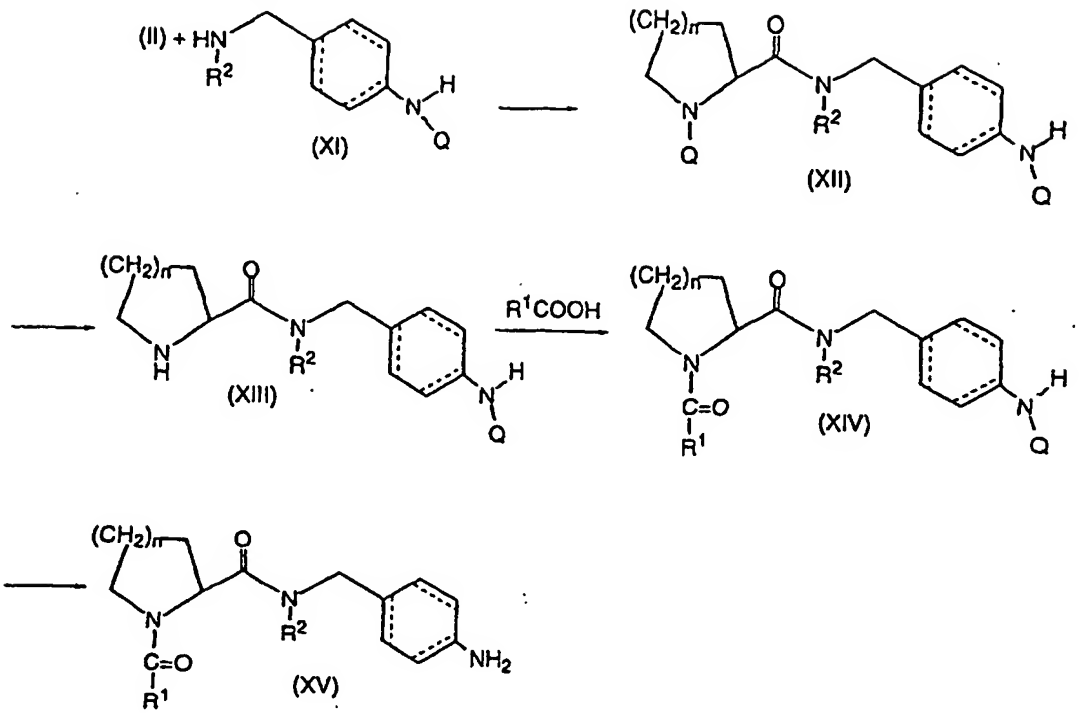
[0019] Hereinafter, the production process for the compounds of the present invention will be explained.

[0020] The compounds of the present invention can be produced through any combination of reactions suitable for the objective compounds. Typical reaction schemes will be shown below, but they should not be construed to be limiting the scope of the present invention.

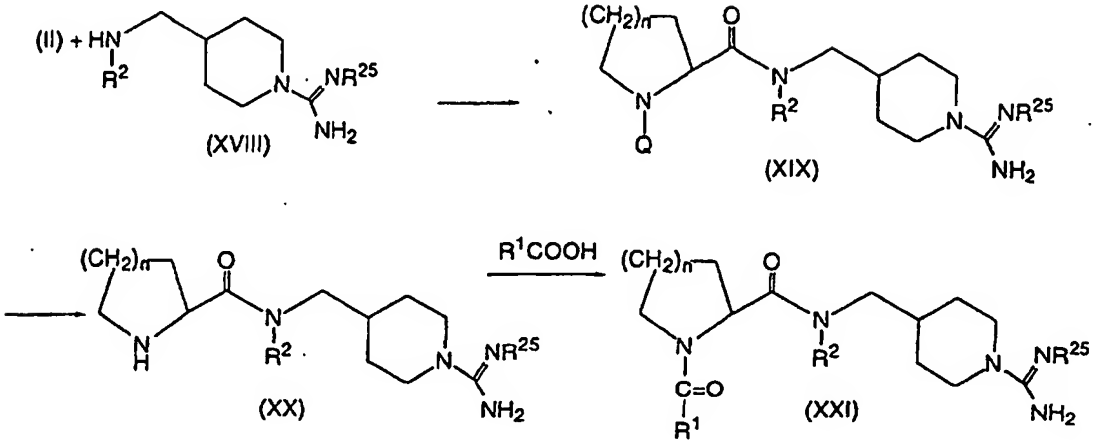
(Reaction scheme I)



(Reaction scheme II)



(Reaction scheme III)



wherein R^1, R^2, R^{25}, n and broken line are as defined above; Q is an aminoprotecting group, such as benzyloxycarbonyl group, tertiary butyloxycarbonyl group, etc.; Z is a leaving group such as halogen atom, methanesulfonyloxy group, toluenesulfonyloxy group, trifluoromethylsulfonyloxy group, acetoxy (acetyloxy) group, etc.

[0021] In the above reaction schemes, a known method for synthesizing amide can be used for synthesizing the compounds (IV), (VI), (XII), (XIV), (XIX) and (XXI). There are various conventional methods, for example, a method using dehydrating agents such as dicyclohexylcarbodiimide, 1-ethyl-3-(dimethylaminopropyl)carbodiimide, carbonyldiimidazole, etc., azido method, acid halide method, acid anhydride method, active ester method and the like.(e.g., see, "JIKKEN KAGAKU KOZA, 22, YUKI-GOSEI IV", pp. 259 - (1992), ed. "JAPAN Chemical Society", 4th. edition,

published by Maruzen). The reaction is conducted under cooling or heating (or at room temperature) using an inert solvent such as tetrahydrofuran, diethyl ether, dichloromethane, etc. in a conventional manner. In the above schemes, the compounds (V), (XIII), (XV) and (XX) can be synthesized by deprotection according to a method known in the peptide chemistry (e.g. see "The Principle and Experimental Procedures of Peptide Synthesis" written by Nobuo IZUMIYA et al., published by Maruzen).

[0022] Further, the compound (VII) is synthesized by reacting imidate, which is obtained by reacting the compound (VI) with alcohol and an inorganic acid such as hydrochloric acid, with ammonia or an ammonium salt; or by reacting a thioamide compound, which is obtained by reacting the compound (VI) with hydrogen sulfide in the presence of an organic base such as triethylamine, pyridine, etc., with a lower alkylhalogen compound such as methyl iodide, etc., followed by reacting the resulting thioimidate compound with ammonia or an ammonium salt. Further, the compound (IX) is synthesized by reacting the compound (VI) with hydroxylamine or acid adduct thereof in a suitable solvent such as water, alcohol, tetrahydrofuran, etc. at room temperature or under heating.

[0023] The respective compounds thus obtained can be isolated and purified by conventional chemical procedures such as extraction, crystallization, recrystallization, various chromatography and the like.

[0024] When the compounds of the present invention are used for clinical application, a proportion of a therapeutically active ingredient to a carrier component varies within a range of 1 to 90% by weight. For example, the compounds of the present invention may be orally administered in the dosage form such as granules, fine granules, powders, tablets, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or intravenously, intramuscularly or subcutaneously administered in the form of injections. Further, they may also be used in the form of suppositories. They may also be formed into powders which can be converted into solutions or the like for injection before use. There can be used pharmaceutical organic or inorganic solid or liquid carriers or diluents which are suitable for oral, intestinal or parenteral administration for preparing the drugs of the present invention. As the excipient used for preparing solid preparations, for example, there can be used lactose, sucrose, starch, talc, cellulose, dextrin, kaoline, calcium carbonate and the like. Liquid preparations for oral administration, i.e. emulsions, syrups, suspensions, solutions, etc. contain inert diluents which are normally used, e.g. water, vegetable oil, etc. This preparation can contain adjuvants such as humectants, suspension auxiliary agents, sweeteners, aromatics, colorants, preservatives, etc., in addition to inert diluents. The resulting liquid preparations may be contained in a capsule of an absorbable substance such as gelatin. As the solvent or suspending agent used for preparing preparations for parenteral administration, i.e. injections, suppositories, etc., for example, there can be used water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. As the base used for preparing suppositories, for example, there can be used cacao butter, emulsified cacao butter, laurin tallow, witepsol and the like. Preparations may be prepared by a conventional method.

[0025] The clinical dose varies depending upon age, pathology, condition of diseases and the like. For example, in the case of administering orally to an adult patient, the compounds of the present invention are normally administered with a dairy dose of about 0.01 to 1000 mg, preferably 10 to 1000 mg. The pharmaceutical composition of the present invention may be administered 1 to 3 times per day or administered intermittently with the above dairy dose.

[0026] When using as injections, it is advantageous that the compounds of the present invention are administered continuously or intermittently to an adult patient with a single dose of 0.001 to 100 mg.

[0027] The prolineamide derivatives of the present invention or the salts thereof have a strong inhibition activity to proteases such as thrombin, trypsin and the like. The compounds of the present invention are also superior in oral absorptive action so that they are useful as oral antithrombin agents, i.e. oral anticoagulants, or oral antitrypsin agents, i.e. remedy for pancreas diseases such as pancreatitis.

[0028] The following Examples and Experimental Examples further illustrate the present invention in detail but are not to be construed to limit the scope thereof.

[0029] The conventional abbreviations used in Examples are as follows: THF:tetrahydrofuran, DMF: N,N-dimethylformamide, DMSO: dimethyl sulfoxide, CDI: carbonyldiimidazole, DPPA: diphenylphosphorylazide, Z: benzyloxycarbonyl, Boc: tertiary butyloxycarbonyl.

[0030] Further, NMR in physical properties stands for a nuclear magnetic resonance spectrum and the numeral is δ value in ppm, which is conventionally used for indicating the chemical shift. TMS (tetramethylsilane) was used as the internal standard. Further, the numeral shown in parenthesis following δ value is the number of hydrogen atoms, and the indications following the number of hydrogen atoms mean that s is singlet, d is doublet, t is triplet, q is quartet, m is multiplet, br is broad absorption peak, respectively.

[0031] IR stands for an infrared spectrum and measured as potassium bromide tablets unless otherwise stated. The numerical means the wave number in cm^{-1}.

[0032] Only main absorption peak was shown. Further, mp means the non-corrected melting point in °C.

Reference Example 1

[0033] Synthesis of 4-amidino-[(S)-N-((R)-2-methylsulfonylaminocyclohexylacetyl) prolyl]aminomethylbenzene

(Reference compound No. 105 of Table 1) hydrochloride.

(a) N-4-cyanobenzylphthalimide

[0034] To a solution of potassium phthalimide (76 g, 410 mmol) in DMF (250 ml), a solution of 4-cyanobenzyl bromide (73 g, 373 mmol) in THF (250 ml) is added and stirred at 50°C for 3 hours.

[0035] Water (500 ml) is added to the mixture and a precipitated crystal was collected. Then, the crystal is washed with water and dried to give 96 g of the titled compound (99%). mp: 189-191°C.

(b) 4-Cyano-[(S)-prolyl]aminomethylbenzene hydrochloride

[0036] To a solution of the compound (39 g, 150 mmol) obtained in the item (a) in methanol (250 ml), hydrazine hydrate (9 ml) is added and refluxed for 6 hours. After the solvent is evaporated, an aqueous 40% sodium hydroxide solution (300 ml) is added to the residue and stirred.

[0037] The reaction mixture is extracted with toluene and the organic layer is washed once with water and saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the resulting crude product (15 g, 73%) is used for the next step.

[0038] To a solution of (S)-N-Boc-proline (23.7 g, 110 mmol) in THF (250 ml), CDI (17.8 g, 110 mmol) is added at 0°C.

[0039] After the reaction solution is stirred for 2 hours, a solution of the crude product obtained in the above reaction in THF (150 ml) is added. After stirring for 6 hours, the solvent is evaporated and water (300 ml) is added to the residue. The mixture is extracted with chloroform and the organic layer is washed three times with water and once with saturated brine, successively. After drying over sodium sulfate, the solvent is evaporated and the residue is purified with silica gel chromatography (hexane-ethyl acetate).

[0040] The resulting oily product is dissolved in ethyl acetate (100 ml) and a 4N-hydrochloride in ethyl acetate (69 ml) is added and the mixture is stirred at 0°C for 3 hours. The precipitated white solid is collected, washed with ethyl acetate and dried under reduced pressure to give 25.9 g of the titled compound (89%).

NMR (DMSO-d^6)

1.80-1.96 (m, 3H), 2.30-2.40 (m, 1H), 3.21 (br, 2H), 4.26 (br, 1H), 4.44 (d, 2H), 7.49 (d, 2H), 7.82 (d, 2H), 8.59 (br, 1H), 9.39 (t, 1H), 10.07 (br, 1H)

(c) 4-Cyano-[(S)-N-((R)-2-t-butyloxycarbonylamino-cyclohexylacetyl) prolyl]aminomethylbenzene

[0041] To a solution of the product (21 g, 79 mmol) obtained in the item (b) and (R)-N-t-butyloxycarbonylcyclohexylglycine (20.4 g, 79 mmol) in DMF (200 ml), a solution of triethylamine (22 ml, 159 mmol) and DPPA (22 g, 79 mmol) in DMF (50 ml) is added at 0°C. The mixture is allowed to stand at room temperature and then stirred for 12 hours. Water (400 ml) is added to the reaction mixture which is extracted with toluene-ethyl acetate (1:2). The organic layer is washed three times with water and once with saturated brine, successively, and then dried over sodium sulfate. After the solvent is evaporated, the residue is purified with silica gel chromatography (chloroform-methanol) to give 26.7 g of the titled compound (72%).

NMR ($CDCl_3$)

1.01-1.43 (m, 15H), 1.65-2.38 (m, 9H), 3.57 (q, 1H), 3.96-4.06 (m, 2H), 4.47 (dq, 2H), 4.69 (d, 1H), 5.12 (d, 1H), 7.35 (d, 2H), 7.59 (d, 2H), 7.73 (t, 1H)

(d) 4-Cyano-[(S)-N-((R)-2-methylsulfonylamino-cyclohexylacetyl)prolyl] aminomethylbenzene

[0042] To a solution of the compound (26.7 g, 57 mmol) obtained in the item (c) in chloroform (50 ml), a 4-N hydrochloride in ethyl acetate (30 ml) is added at 0 °C. The mixture is stirred for 3 hours and then the solvent is evaporated. The resulting residue was dissolved in dichloromethane (250 ml) and triethylamine (19 ml) is added. Then, a solution of methanesulfonyl chloride (7.9 g, 68 mmol) in dichloromethane (50 ml) is added at 0°C and the mixture is stirred for 3 hours. The organic layer is washed once with a saturated sodium bicarbonate solution, water and saturated brine, successively, and then dried over sodium sulfate. The resulting residue is purified with silica gel chromatography (hexane-ethyl acetate) to give 18.6 g of the titled compound (73%).

NMR ($CDCl_3$)

0.9-1.29 (m, 5H), 1.60-1.85 (m, 5H), 2.0-2.4 (m, 5H), 2.89 (s, 3H), 3.55 (q, 1H), 3.80-3.88 (m, 2H), 4.43 (d, 2H), 4.61 (d, 2H), 5.60 (d, 2H), 7.31 (t, 1H), 7.37 (d, 2H), 7.60 (d, 2H)

(e) 4-Amidino-[(S)-N-((R)-2-methylsulfonylamino-cyclohexylacetyl) prolyl]aminomethylbenzene chloride

[0043] To a solution of the compound (18.6 g, 42 mmol) obtained in the item (d) in chloroform (100 ml), a 37% hydrochloride in ethanol (100 ml) is added at 0°C. The mixture is allowed to stand at 0°C for 48 hours and then the solvent is evaporated. The resulting residue is dissolved in methanol (100 ml) and ammonium carbonate (16 g, 166 mmol) is added at 0°C. After stirring for 6 hours, the solvent is evaporated and the resulting residue is purified with silica gel chromatography (chloroform-methanol) to give 5.2 g of the titled compound (73%).
NMR (DMSO-d^6)
9.39 (br, 4H), 8.66 (t, 1H), 7.81 (d, 2H), 7.48 (d, 2H), 7.40 (m, 1H), 4.47-4.14 (m, 3H), 3.90 (m, 1H), 3.71 (m, 1H), 3.59 (m, 1H), 2.79 (s, 3H), 2.13 (m, 1H), 1.88 (m, 3H), 1.69-1.53 (m, 5H), 1.14 (m, 6H)
IR: 3366, 2930, 2855, 1636, 1541, 1489, 1451, 1152

[0044] According to the same procedures described above, the compounds shown in the following Examples were synthesized.

Example 1

[0045] 4-Amidino-[(S)-N-((R)-N'-formylphenylalanyl) prolyl] aminomethylbenzene (compound No. 94 of Table 1) hydrochloride NMR (DMSO-d^6)
9.56 (br, 2H), 9.36 (br, 2H), 8.97 (t, 1H), 8.70 - 8.60 (m, 1H), 7.86 (d, 1H), 7.83 (d, 2H), 7.46 (d, 2H), 7.37-7.17 (m, 5H), 4.36-4.16 (m, 4H), 3.60 - 2.70 (m, 4H), 2.40-1.20 (m, 4H)
IR: 3370, 1647, 1541, 1489, 1454, 1404, 704

Example 2

[0046] 4-Amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-3-methyl-3-methylthiobutanoyl] prolyl]aminomethylbenzene (compound No. 98 of Table 1) hydrochloride
NMR (DMSO-d^6)
8.89 (br, 2H), 8.66 (br, 2H), 7.77 (d, 2H), 7.33 (d, 2H), 6.27 (d, 1H), 4.65 (m, 1H), 4.46 (d, 1H), 4.37 (m, 2H), 3.97-3.72 (m, 4H), 2.62 (m, 1H), 2.15 (br, 3H), 2.04 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.05 (t, 3H)
IR: 3323, 2926, 1635, 1535, 1439, 1242, 1055

Example 3

[0047] 4-Amidino-[(S)-N-(4-phenylbutanoyl)prolyl] aminomethylbenzene (compound No. 3 of Table 1) hydrochloride
NMR (DMSO-d^6)
9.39 (br, 2H), 9.22 (br, 2H), 8.55 (t, 1H), 7.80 (d, 2H), 7.48 (d, 2H), 7.31-7.13 (m, 5H), 4.37-4.30 (m, 3H), 3.60-3.30 (m, 2H), 2.60 (t, 2H), 2.34-1.75 (m, 8H)
IR: 3264, 1618, 1541, 1491, 1451, 702

Example 4

[0048] 4-Amidino-[(S)-N-(2-benzyloxyacetyl)prolyl] aminomethylbenzene (compound No. 55 of Table 1) hydrochloride
NMR (DMSO-d^6)
9.41 (br, 2H), 9.23 (br, 2H), 8.66 (t, 1H), 7.80 (d, 2H), 7.49 (d, 2H), 7.42-7.27 (m, 5H), 4.61-4.08 (m, 7H), 3.56-3.40 (m, 2H), 2.20-1.78 (m, 4H)
IR: 3262, 1645, 1539, 1489, 1454, 740

Example 5

[0049] Trans-4-amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl]prolyl] aminomethylcyclohexane (compound No. 263 of Table 1) hydrochloride

(a) Trans-4-N-benzyloxycarbonylaminomethyl-cyclohexylnitrile

[0050] To a solution of trans-4-aminomethylcyclohexanecarboxylic acid (25 g, 159 mmol) and sodium carbonate (20 g, 191 mmol) in water (300 ml), benzyloxycarbonyl chloride (27 ml, 190 mmol) is added at 0°C. After stirring for 6 hours, 1N-hydrochloric acid is added until the pH of the reaction mixture indicates 2, and the precipitated white solid is col-

lected, washed with water and dried. The resulting white solid is dissolved in THF (300 ml) and CDI (21 g, 130 mmol) is added at 0°C. After stirring for 3 hours, the reaction mixture is added dropwise to a mixed solution of 33% ammonia in water (50 ml) and THF (150 ml) at 0°C. After stirring for 5 hours, the solvent is evaporated and water (500 ml) is added, and the precipitated white solid is collected, washed with water and dried.

[0051] To a solution of the resulting compound in 1,2-dichloroethane (500 ml), thionyl chloride (19 ml, 260 mmol) is added and heated to an inner temperature of 70°C. After stirring for 5 hours, the reaction mixture is poured into ice water and neutralized with an aqueous 1N-sodium hydroxide solution. After extracting with chloroform, the organic layer is washed twice with water and once with saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the resulting crude product is recrystallized (hexane-ethyl acetate) to give 22.8 g of the titled compound (53%). mp: 90-92°C

(b) Trans-4-(S)-prolylaminomethyl-cyclohexylnitrile

[0052] The compound obtained in the item (a) is dissolved in ethanol (250 ml) and the catalytic hydrogenation is conducted at room temperature and atomospheric pressure in the presence of palladium black (1 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated.

[0053] To a solution of (S)-N-benzyloxycarbonylproline (20.7 g, 83 mmol) in THF (150 ml), CDI (13.5 g, 83 mmol) is added at 0'C. After stirring for 3 hours, a solution of the compound obtained in the above reaction in THF (200 ml) is added at 0°C. After stirring for 12 hours, the solvent is evaporated, and chloroform (400 ml) is added to the resulting residue. The organic layer is washed three times with water and once with saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the resulting residue is purified with silica gel chromatography (chloroform-methanol).

[0054] The resulting compound is dissolved in ethanol (250 ml) and the catalytic hydrogenation is conducted at room temperature and atomospheric pressure in the presence of palladium black (1 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated to give 18.8 g of the titled compound (95%).

NMR (DMSO-d^6)

0.88-1.06 (m, 2H), 1.38-1.52 (m, 3H), 1.68-2.03 (m, 7H), 2.20-2.40 (m, 1H), 2.52-2.67 (m, 1H), 2.80-3.20 (m, 4H), 4.03-4.10 (m, 1H), 7.53 (br, 1H), 8.65-8.70 (m, 1H)

(c) Trans-4-amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexane hydrochloride

[0055] According to the same manner as that described in the items (c) to (e) of Example 1, the titled compound can be synthesized from the compound obtained in the item (b) and (R)-2-t-butyloxycarbonylamino-4,4-dimethylpentanoic acid.

NMR (DMSO-d^6)

8.95 (br, 2H), 8.69 (br, 2H), 7.60 (br, 1H), 6.32 (br, 1H), 4.56 (m, 1H), 4.39 (m, 1H), 4.18 (q, 2H), 4.10 (m, 1H), 3.52 (m, 1H), 3.19 (m, 1H), 2.89 (m, 1H), 2.69 (m, 1H), 2.14-1.59 (m, 12H), 1.26 (t, 3H), 0.98 (s, 9H), 0.98-0.89 (m, 2H)

IR: 3314, 2954, 1686, 1639, 1543, 1449, 1250, 1059

[0056] According to the same procedures, the compounds shown in the following Examples were synthesized.

Example 6

[0057] Trans-4-amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-3-cyclohexylpropanoyl] prolyl]aminoethylcyclohexane (compound No. 227 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.93 (br, 2H), 8.81 (br, 2H), 7.53 (br, 1H), 7.38 (t, 1H), 4.50-4.15 (m, 1H), 4.10-3.90 (m, 2H), 3.73-3.17 (m, 2H), 3.05-2.80 (m, 3H), 2.39 (br, 1H), 2.00-0.68 (m, 29H)

IR: 3297, 2926, 2853, 1684, 1543, 1449, 1262, 1053

Example 7

[0058] Trans-4-amidino-[(S)-N-[(R)-2-isopropoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexane (compound No. 265 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.91 (br, 2H), 8.78 (br, 2H), 7.55 (br, 1H), 7.28 (t, 1H), 4.78-4.70 (m, 1H), 4.30-3.92 (m, 1H), 3.80-3.20 (m, 3H), 3.0-2.75 (m, 2H), 2.50-1.37 (m, 14H), 1.18-1.00 (m, 6H), 1.0-0.81 (m, 1H)

IR: 3285, 2953, 2870, 1684, 1541, 1449, 1250, 1111

Example 8

[0059] Trans-4-amidino-[(S)-N-((R)-2-isopropoxycarbonylamino-2-cyclohexylacetyl) prolyl]aminomethylcyclohexane (compound No. 228 of Table 1) hydrochloride
NMR (DMSO-d^6)
8.91 (br, 2H), 8.69 (br, 2H), 7.36 (br, 1H), 5.99 (d, 1H), 4.84-4.79 (m, 1H), 4.58 (br, 2H), 4.53-4.50 (m, 2H), 4.10-3.90 (m, 2H), 3.60-3.40 (m, 1H), 2.50-0.97 (m, 30H)
IR: 3297, 2980, 2930, 2855, 1684, 1539, 1451, 1258

Example 9

[0060] Trans-4-amidino-[(S)-N-((R)-2-ethoxycarbonylamino-4-ethyl-hexanoyl) prolyl]aminomethylcyclohexane (compound No. 264 of Table 1) hydrochloride
NMR (DMSO-d^6)
8.91 (br, 2H), 8.70 (br, 2H), 7.54 (m, 1H), 6.34 (m, 1H), 4.56 (m, 1H), 4.38 (m, 1H), 4.11 (m, 3H), 3.48 (m, 1H), 3.21 (m, 1H), 2.88 (m, 1H), 2.68 (m, 1H), 2.30-1.19 (m, 18H), 1.26 (t, 3H), 0.96 (m, 2H), 0.86 (t, 6H)
IR: 3279, 2962, 1685, 1639, 1541, 1448, 1257, 1059, 752

Example 10

[0061] Trans-4-amidino-[(S)-N-[(R)-2-t-butoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexane (compound No. 266 of Table 1) glycolate
NMR (DMSO-d^6)
9.54 (br, 2H), 8.72 (br, 2H), 7.54 (br, 1H), 7.01 (t, 1H), 4.60-4.00 (m, 4H), 3.40 (m, 2H), 3.10-2.75 (m, 3H), 2.35 (br, 1H), 2.00-1.20 (m, 24H), 0.91 (s, 9H)
IR: 3316, 2953, 1686, 1543, 1449, 1368, 1167

Example 11

[0062] 4-[(S)-N-[(R)-2-t-butyloxycarbonylamino-cyclohexylacetyl] prolyl] aminomethyl-benzamidoxime (compound No. 396 of Table 1)
[0063] To a solution of the compound (0.94 g, 2 mmol) obtained in the item (c) of Example 1 in ethanol (15 ml), a solution of sodium carbonate (0.17 g, 1.6 mmol) in water (3 ml) and hydroxyamine hydrochloride (0.22 g, 3.2 mmol) are added. After the reaction mixture is heated at reflux for 8 hours, the solvent is evaporated and the resulting residue is purified with silica gel column chromatography (chloroform-methanol) to give 0.84 g of the titled compound (84%).
NMR ($CDCl_3$)
1.0-1.49 (m, 14H), 1.5-2.4 (m, 10H), 3.56 (br, 1H), 3.97 (br, 1H), 4.09 (t, 1H), 4.41 (dq, 2H), 4.67 (d, 1H), 4.94 (br, 2H), 5.41 (d, 1H), 7.20 (d, 2H), 7.23-7.27 (m, 1H), 7.50 (d, 2H), 7.75 (br, 1H)
IR: 3345, 2978, 2930, 2855, 1640, 1528, 1449, 1167
[0064] According to the same procedures, the compounds shown in the following Examples were synthesized.

Example 12

[0065] 4-[(S)-N-phenylacetylprolyl] aminomethyl-benzamidoxime (compound No. 374 of Table 1)
NMR ($CDCl_3$)
8.11 (t, 1H), 7.37 (d, 2H), 7.28-7.23 (m, 5H), 7.08 (d, 2H), 4.88 (s, 2H), 4.68 (d, 1H), 4.51 (m, 1H), 4.21 (m, 1H), 3.71 (s, 2H), 3.63-3.51 (m, 2H), 2.40-2.01 (m, 4H)
IR: 3315, 2968, 1637, 1543, 1244, 1155, 927, 709

Example 13

[0066] 4-[(S)-N-[(R)-N'-ethoxycarbonylphenylalanyl] prolyl]aminomethylbenzamidoxime (compound No. 387 of Table 1)
NMR ($CDCl_3$)
7.54 (d, 2H), 7.27-7.19 (m, 7H), 6.31 (d, 1H), 5.05 (br, 2H), 4.65-4.42 (m, 3H), 4.24-4.10 (m, 1H), 3.80-3.40 (m, 3H), 3.10-2.95 (m, 2H), 2.60-2.50 (m, 1H), 2.14 (br, 1H), 1.95-1.50 (m, 3H), 0.99 (t, 3H)
IR: 3339, 1641, 1539, 1451, 1260, 752, 702

Example 14

[0067] 4-[(S)-N-[(R)-2-t-butyloxycarbonylamino-3-cyclohexylpropanoyl] prolyl]aminomethyl-benzamidoxime (compound No. 397 of Table 1)
NMR ($CDCl_3$)
7.75 (br, 1H), 7.50 (d, 2H), 7.21 (d, 2H), 5.40 (d, 1H), 4.94 (br, 2H), 4.64 (br, 1H), 4.40-4.25 (m, 3H), 3.95 (br, 1H), 3.50-3.40 (m, 1H), 2.0-0.80 (m, 26H)
IR: 3337, 2978, 2924, 2851, 1642, 1536, 1449, 1167

Example 15

[0068] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-3-methyl-3-methylthlobutanoyl] prolyl]aminomethyl-benzamidoxime (compound No. 419 of Table 1)
NMR ($CDCl_3$)
7.66 (t, 1H), 7.53 (d, 2H), 7.23 (d, 2H), 5.64 (d, 1H), 4.91 (s, 2H), 4.68 (d, 1H), 4.58-4.30 (m, 3H), 3.90 (m, 1H), 3.87-3.76 (m, 2H), 3.62 (m, 1H), 2.37 (m, 1 H), 2.09-2.00 (m, 3H), 2.06 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.09 (t, 3H)
IR: 3339, 2978, 1641, 1535, 1439, 1249, 1057, 929, 754

Example 16

[0069] 4-[(S)-N-[(R)-phenylalanyl] prolyl]aminomethyl-benzamidoxime (compound No. 390 of Table 1) dihydrochloride
NMR (DMSO-d^6)
11.24 (br, 1H), 9.02 (br, 2H), 8.91 (t, 1H), 8.80 (br, 3H), 7.66 (d, 2H), 7.44 (d, 2H), 7.35-7.22 (m, 5H), 4.30-4.16 (m, 4H), 3.57-2.95 (m, 3H), 2.45-2.30 (m, 1H), 1.90-1.20 (m, 4H)
IR: 3059, 1649, 1539, 1491, 1454

Example 17

[0070] Trans-4-[(S)-N-((R)-2-isopropoxycarbonylamino-2-cyclohexylacetyl) prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 430 of Table 1)
NMR ($CDCl_3$)
7.14 (br, 1H), 5.70 (d, 1H), 4.85-4.80 (m, 1H), 4.70-4.50 (m, 3H), 4.17-4.08 (m, 2H), 3.96 (br, 1H), 3.54 (q, 1H), 3.05 (t, 2H), 2.40-2.20 (m, 1H), 2.09-0.88 (m, 30H)
IR: 3342, 2978, 2928, 2855, 1653, 1449, 1256, 1111

Example 18

[0071] Trans-4-[(S)-N-((R)-2-t-butoxycarbonylamino-3-cyclohexylpropanoyl) prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 435 of Table 1)
NMR ($CDCl_3$)
7.14 (br, 1H), 5.40 (d, 1H), 4.60-4.33 (m, 5H), 3.88 (br, 1H), 3.43 (q, 1H), 3.20-3.11 (m, 1H), 3.0-2.96 (m, 1H), 2.40-2.30 (m, 1H), 2.0-0.84 (m, 35H)
IR: 3356, 2926, 2853, 1649, 1537, 1448, 1167

Example 19

[0072] Trans-4-[(S)-N-((R)-2-t-butoxycarbonylamino-2-cyclohexylacetyl) prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 433 of Table 1)
NMR ($CDCl_3$)
7.15 (br, 1H), 5.28 (d, 1H), 4.58 (br, 4H), 4.09 (t, 1H), 3.92 (br, 1H), 3.53 (q, 1H), 3.20-2.90 (m, 2H), 2.40 (br, 1H), 2.10-0.91 (m, 33H)
IR: 3347, 2930, 2855, 1649, 1541, 1451, 1169

Example 20

[0073] Trans-4-[(S)-N-[(R)-2-t-ethoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 461 of Table 1)

NMR ($CDCl_3$)
7.06 (t, 1H), 5.56 (d, 1H), 4.57-4.39 (m, 4H), 4.11 (q, 2H), 3.98 (m, 1H), 3.47 (m, 1H), 3.05 (m, 2H), 2.39 (m, 1H), 2.04-1.78 (m, 10H), 1.57 (d, 2H), 1.56-1.12 (m, 2H), 1.24 (t, 3H), 0.99 (s, 9H), 0.99-0.89 (m, 2H)
IR: 3356, 2934, 1649, 1541, 1446, 1249, 1059, 927

Example 21

[0074] Trans-4-[(S)-N-[(R)-2-methoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 458 of Table 1)
NMR ($CDCl_3$)
7.04 (t, 1H), 5.53 (d, 1H), 4.68 (s, 2H), 4.56 (d, 1H), 4.43 (m, 1H), 3.98 (m, 1H), 3.66 (s, 3H), 3.47 (m, 1H), 3.07 (m, 2H), 2.39 (m, 1H), 2.19-1.77 (m, 8H), 1.57 (d, 2H), 1.55-1.25 (m, 4H), 0.99 (s, 9H), 0.93 (m, 2H)
IR: 3344, 2949, 1712, 1649, 1548, 1448, 1249, 1059

Example 22

[0075] Trans-4-[(S)-N-[(R)-2-t-butoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 467 of Table 1)
NMR ($CDCl_3$)
7.12 (t, 1H), 5.14 (d, 1H), 4.58 (d, 1H), 4.53 (s, 2H), 4.37 (m, 1H), 3.92 (m, 1H), 3.45 (m, 1H), 3.19 (m, 1H), 2.95 (m, 1H), 2.42 (m, 1H), 2.06-1.79 (m, 8H), 1.53 (d, 2H), 1.52-1.34 (m, 4H), 1.43 (s, 9H), 0.99 (s, 9H), 1.00-0.89 (m, 2H)
IR: 3358, 2930, 1649, 1535, 1448, 1367, 1249, 1168

Example 23

[0076] Trans-4-[(S)-N-[(R)-2-benzyloxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 469 of Table 1)
NMR ($CDCl_3$)
7.36-7.27 (m, 5H), 7.04 (t, 1H), 5.63 (d, 1H), 5.16-5.00 (m, 2H), 4.58-4.46 (m, 4H), 3.97 (m, 1H), 3.47 (m, 1H), 3.06-2.92 (m, 2H), 2.43-2.38 (m, 1H), 2.01-1.72 (m, 8H), 1.58 (d, 2H), 1.50-1.23 (m, 4H), 0.98 (s, 9H), 0.98-0.88 (m, 2H)
IR: 3356, 2928, 1649, 1541, 1448, 1249, 1053 929

Example 24

[0077] Trans-4-[(S)-N-[(R)-2-isopropoxycarbonylamino-4,4-dimethylpentanoyl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 464 of Table 1)
NMR ($CDCl_3$)
7.11 (t, 1H), 5.49 (d, 1H), 4.83 (m, 1H), 4.56 (m, 3H), 4.42 (dd, 1H), 3.98 (m, 1H), 3.47 (dd, 1H), 3.04 (m, 2H), 2.40 (m, 1H), 2.01 (m, 2H), 1.92 (m, 3H), 1.80 (m, 3H), 1.57 (d, 2H), 1.39 (m, 4H), 1.21 (m, 6H), 0.99 (s, 9H), 0.94 (m, 2H)
IR: 3343, 1649, 1541, 1449, 1275

Example 25

[0078] Trans-4-[(S)-N-[(R)-2-isopropoxycarbonylamino-2-cyclopentylacetyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 429 of Table 1)
NMR ($CDCl_3$)
7.14 (t, 1H), 5.42 (d, 1K), 4.83 (m, 1H), 4.60 (d, 1H), 4.52 (s, 2H), 4.13 (m, 1H), 3.98 (m, 1H), 3.56 (m, 1H), 3.04 (m, 2H), 2.35 (m, 1H), 2.24 (m, 1H), 2.10-1.30 (m, 20H), 1.23 (dd, 6H), 1.01-0.93 (m, 2H)
IR: 3344, 2934, 1649, 1541, 1448, 1275, 1111, 754

Example 26

[0079] Trans-4-[(S)-N-((R)-2-t-butoxycarbonylamino-2-cyclopentylacetyl) prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 432 of Table 1)
NMR ($CDCl_3$)
7.16 (t, 1H), 5.16 (d, 1H), 4.60 (d, 1H), 4.51 (s, 2H), 4.14 (t, 1H), 3.94 (m, 1H), 3.52 (m, 1H), 3.01 (m, 2H), 2.38 (m, 1H), 2.23-1.39 (m, 21H), 1.43 (s, 9H), 1.17-0.90 (m, 2H)
IR: 3350, 2932, 1649, 1541, 1448, 1367, 1251, 1167, 929

Example 27.

[0080] Trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-3-cyclohexylpropanoyl) prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 428 of Table 1)
NMR ($CDCl_3$)
7.08 (br, 1H), 5.53 (d, 1H), 4.80-4.40 (m, 4H), 4.10-3.85 (m, 4H), 3.44 (q, 1H), 3.06 (t, 3H), 2.15-0.90 (m, 29H)
IR: 3343, 2926, 2853, 1649, 1541, 1449, 1260, 1053

Example 28

[0081] Trans-4-[(S)-N-((R)-2-isopropoxycarbonylamino-3-cyclohexylpropanoyl) prolyl] aminomethylcyclohexanecarboxamidoxime
(compound No. 431 of Table 1)
NMR ($CDCl_3$)
7.12 (br, 1H), 5.51 (d, 1H), 4.85-4.70 (m, 1H), 4.60-4.30 (m, 4H), 4.0-3.85 (m, 1H), 3.44 (q, 1H), 3.10-2.95 (m, 3H), 2.45-2.35 (m, 1H), 2.05-0.80 (m, 32H) IR: 3347, 2978, 2926, 2853, 1649, 1539, 1449, 1261, 1111

Example 29

[0082] Trans-4-[(S)-N-((R)-2-isopropoxycarbonylamino-4-ethyl-hexanoyl) prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 463 of Table 1)
NMR ($CDCl_3$)
7.11 (t, 1H), 5.41 (d, 1H), 4.83 (m, 1H), 4.56 (m, 3H), 4.39 (m, 1H), 3.94 (m, 1H), 3.46 (m, 1H), 3.02 (m, 2H), 2.39 (m, 1H), 2.10-1.20 (m, 20H), 1.22 (dd, 6H), 1.02-0.84 (m, 2H), 0.86 (t, 6H)
IR: 33346, 2962, 2930, 1653, 1541, 1448, 1271, 1113

Example 30

[0083] Trans-4-[(S)-N-((R)-2-t-butoxycarbonylamino-4-ethyl-hexanoyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 466 of Table 1)
NMR ($CDCl_3$)
7.19 (t, 1H), 5.14 (d, 1H), 4.60 (d, 1H), 4.50 (s, 2H), 4.33 (m, 1H), 3.89 (m, 1H), 3.43 (m, 1H), 3.15 (m, 1H), 2.95 (m, 1H), 2.40 (m, 1H), 2.10-1.19 (m, 20H), 1.43 (s, 9H), 1.04-0.89 (m, 2H), 0.86 (t, 6H)
IR: 3346, 2964, 2930, 1649, 1541, 1448, 1367, 1280, 1251, 1168, 929

Example 31

[0084] Trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-heptanoyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 459 of Table 1)
NMR ($CDCl_3$)
7.08 (t, 1H), 5.60 (d, 1H), 4.58 (m, 3H), 4.35 (m, 1H), 4.07 (m, 2H), 3.92 (m, 1H), 3.48 (m, 1H), 3.06 (m, 2H), 2.40 (m, 1H), 2.04-1.32 (m, 20H), 1.24 (t, 3H), 0.89 (t, 3H), 0.98 (m, 2H)
IR: 3346, 2928, 1649, 1541, 1448, 1255, 1055, 927

Example 32

[0085] Trans-4-[(S)-N-((R)-N'-t-butoxycarbonylamino-methionyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 468 of Table 1) NMR ($CDCl_3$)
7.07 (m, 1H), 5.31 (d, 1H), 4.55 (m, 4H), 3.56 (m, 1H), 3.10 (m, 2H), 2.57 (t, 2H), 2.37 (m, 1H), 2.11 (s, 3H), 2.06-1.29 (m; 14H), 1.43 (s, 9H), 1.00 (m, 2H)
IR: 3354, 2928, 1647, 1541, 1448, 1367, 1251, 1167

Example 33

[0086] Trans-4-[(S)-N-((R)-2-hydroxy-4,4-dimethyl-pentanoyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 454 of Table 1)
NMR ($CDCl_3$)
7.19 (t, 1H), 4.68 (s, 2H), 4.50 (d, 1H), 4.36 (1, 1H), 3.64 (t, 1H), 3.39 (m, 1H), 3.06 (m, 2H), 2.35 (m, 2H),

2.16-1.79 (m, 9H), 1.44 (d, 2H), 1.43-1.25 (m, 3H), 1.00-0.95 (m, 2H), 1.02 (s, 9H)
IR: 3337, 2944, 1653, 1620, 1566, 1448, 1386, 1248, 1087

Example 34

[0087] Trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-4-ethyl-hexanoyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 460 of Table 1)
NMR ($CDCl_3$)
7.07 (t, 1H), 5.53 (d, 1H), 4.56 (m, 3H), 4.40 (m, 1H), 4.11 (q, 2H), 3.96 (m, 1H), 3.45 (m, 1H), 3.05 (m, 2H), 2.36 (m, 1H), 2.09-1.77 (m, 10H), 1.61-1.21 (m, 8H), 1.24 (t, 3H), 1.02-0.83 (m, 2H), 0.86 (t, 6H)
IR: 3342, 2962, 2930, 1649, 1541, 1448, 1379, 1269, 1059, 929

Reference Example 2

[0088] Trans-4-amino-[(S)-N-[(R)-N'-methanesulfonylphenyalanyl] prolyl] aminomethylcyclohexane (Reference compound No. 776 of Table 1) L-tartrate.

(a) Trans-4-t-butyloxycarbonylamino-benzyloxycarbonylaminomethylcyclohexane

[0089] To a solution of trans-4-aminomethylcyclohexanecarboxylic acid (15.7 g, 100 mmol) and sodium hydroxide (4.0 g, 100 mmol) in water (30 ml), benzyloxycarbonyl chloride (15.6 ml, 110 mmol) and sodium hydroxide (4.4 g, 110 mmol) in water (30 ml) are added dropwise at 0°C, simultaneously. After stirring for 4 hours, the mixture is extracted once with ether and 1 N-hydrochloric acid is added to the aqueous layer until the pH of the mixture indicates 2. Then, the precipitated white solid is collected and dried.

[0090] To a solution of the resulting compound (12.8 g, 50 mmol) in t-butanol (150 ml), triethylamine (8.3 ml, 60 mmol) and DPPA (13.7 g, 50 mmol) are added and heated at reflux for 8 hours. After the solvent is evaporated, water is added to the residue and the mixture is extracted with chloroform. The organic layer is washed once with an aqueous sodium carbonate (5%), once with an aqueous potassium hydrogensulfate (5%), twice with water and once with saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the residue is purified with silica gel column chromatography (hexane-ethyl acetate) to give 8.6 g of the titled compound (47%).
NMR ($CDCl_3$)
0.85-1.37 (m, 14H), 1.60-1.85 (m, 4H), 2.84 (t, 1H), 3.12 (br, 1H), 5.00 (s, 2H), 6.62 (d, 1H), 7.23-7.39 (m, 6H)

(b) Trans-4-t-butyloxycarbonylamino-[(S)-N-benzyloxycarbonylprolyl] aminomethylcyclohexane

[0091] The compound (4.4 g, 12 mmol) obtained in the item (a) is dissolved in methanol (200 ml) and the catalytic hydrogenation is conducted at room temperature and under atomospheric pressure in the presence of palladium black (0.4 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated.

[0092] To a solution of (S)-Z-proline (3.0 g, 12 mmol) in THF (30 ml), CDI (2.0 g, 12 mmol) is added at 0°C. After stirring for 3 hours, a solution of the compound obtained in the above reaction in THF (150 ml) is added at 0°C. After stirring for 6 hours, the solvent is evaporated and water (50 ml) is added to the residue. The mixture is extracted with chloroform and the organic layer is washed three times with water and once with saturated brine, successively. After drying over sodium sulfate, the solvent is evaporated and the residue is purified with silica gel chromatography (chloroform-methanol) to give 4.2 g of the titled compound (77%).
NMR ($CDCl_3$)
0.85-1.06 (m, 4H), 1.44 (s, 9H), 1.60-2.35 (m, 9H), 2.94-3.20 (m, 2H), 3.20-3.55 (m, 3H), 4.31 (br, 1H), 4.47 (br, 1H), 5.14 (s, 2H), 6.90 (br, 1H), 7.15-7.40 (m, 5H)

(c) Trans-4-t-butyloxycarbonylamino-[(S)-N-[(R)-N'-benzyloxycarbonylphenylalanyl] prolyl] aminomethylcyclohexane

[0093] The compound (3.6 g, 7.9 mmol) obtained in the item (b) is dissolved in methanol (50 ml) and the catalytichydrogenation is conducted at room temperature and under atomospheric pressure in the presence of palladium black (0.3 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated.

[0094] To a solution of (R)-Z-phenylalanine (2.4 g, 7.9 mmol) in THF (30 ml), CDI (1.3 g, 7.9 mmol) is added at 0°C. After stirring for 4 hours, a solution of the compound obtained in the above reaction in THF (60 ml) is added. After stirring for 8 hours, the solvent is evaporated and water is added to the reaction mixture. The mexture is extracted with chloroform and the organic layer is washed three times with water and once with saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the residue is purified with silica gel column chroma-

tography (chloroform-methanol) to give 4.2 g of the titled compound (89%). NMR ($CDCl_3$)

0.85-1.06 (m, 5H), 1.33-2.0 (m, 15H), 2.10-2.22 (m, 1H), 2.50-2.60 (m, 1H), 2.94-3.01 (m, 5H), 3.30 (br, 1H), 3.57 (t, 1H), 4.32-4.59 (m, 3H), 5.08 (d, 2H), 5.69 (d, 1H), 7.02 (br, 1H), 7.18-7.37 (m, 10H)

(d) Trans-4-amino-[(S)-N-[(R)-N'-methanesulfonylphenylalanyl]prolyl] aminomethylcyclohexane L-tartrate.

[0095] The compound (2.4 g, 3.9 mmol) obtained in the item (c) is dissolved in methanol (40 ml) and the catalytic hydrogenation is conducted at room temperature and under atomospheric pressure in the presence of palladium black (0.2 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated. To a solution of the resulting compound in dichloromethane (40 ml), triethylamine (0.65 ml, 4.7 mmol) is added and a solution of methanesulfonyl chloride (0.47 g, 4.1 mmol) in dichloromethane (100 ml) is further added at 0°C. After stirring for 3 hours, an aqueous saturated sodium bicarbonate solution is added and the organic layer is washed once with water and saturated brine, successively. After drying over sodium sulfate, the solvent is evaporated and the residue is purified with silica gel chromatography (chloroform-methanol),

[0096] The resulting compound is dissolved in chloroform (10 ml) and a 4N-dioxane hydrochloride in dioxane (10 ml) is added at 0°C. After stirring for 2 hours, the solvent is evaporated and chloroform (10 ml) and a 1N-sodium hydroxide solution (10 ml) are added to the residue and, further, the mixture is stirred for 10 minutes. The organic layer is dried over sodium sulfate and a solution of L-tartaric acid (0.34 g, 2.26 nm) in methanol (5 ml) is added.

[0097] The solvent is evaporated and ether (20 ml) is added, and then the precipitated white solid is collected and dried to give 1.36 g of the titled compound (58%).

NMR (DMSO-d^6)

7.77 (m, 4H), 7.28 (m, 5H), 4.28 (m, 1H), 4.16 (m, 1H), 3.57-3.45 (m, 8H), 2.73 (s, 3H), 1.91-1.75 (m, 9H), 1.54 (m, 1H), 1.25 (m, 4H), 0.93 (m, 2H)

IR: 3324, 2934, 1734, 1638, 1545, 1453, 1308, 1148

[0098] According to the same procedures, the compounds shown in the following Examples were synthesized.

Example 35

[0099] Trans-4-amino-[(S)-N-((RS)-3-methylsulfonylamino-3-phenylpropanoyl) prolyl]aminomethylcyclohexane (compound No. 777 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.08 (m, 3H), 7.34 (m, 5H), 4.78 (m, 1H), 4.15 (m, 2H), 3.51 (m, 1H), 3.36 (m, 2H), 2.86 (m, 4H), 2.68 (s, 3H), 2.51 (m, 2H), 2.00-1.69 (m, 6H), 1.27 (m, 4H), 0.92 (m, 2H)

IR: 3409, 2936, 1638, 1453, 1314, 1148

Example 36

[0100] Trans-4-amino-[(S)-N-((R)-2-isopropoxycarbonylamino-4,4-dimethylpentanoyl) prolyl]aminomethylcyclohexane (compound No. 797 of Table 1)

NMR ($CDCl_3$)

7.19 (m, 1H), 5.32 (d, 1H), 4.82 (m, 1H), 4.53 (m, 2H), 4.00 (m, 1H), 3.48 (m, 1H), 3.03-2.16 (m, 6H), 2.00-1.81 (m, 6H), 1.57 (d, 2H), 1.49 (m, 4H), 1.24 (m, 6H), 1.00 (s, 9H), 0.95 (m, 2H)

IR: 3326, 2949, 1640, 1541, 1449, 1248

Example 37

[0101] Trans-4-amino-[(S)-N-((R)-N'-ethoxycarbonyl-phenylalanyl) prolyl] aminomethylcyclohexane (compound No. 780 of Table 1) hydrochloride

NMR (DMSO-d^6)

7.98 (m, 3H), 7.37 (t, 1H), 7.26 (m, 5H), 4.37 (dd, 1H), 4.16 (m, 1H), 4.02 (m, 2H), 3.88 (m, 1H), 3.59 (m, 1H), 3.43 (m, 1H), 2.86 (m, 5H), 1.93-1.75 (m, 7H), 1.28 (m, 4H), 1.15 (t, 3H), 0.92 (m, 2H)

IR: 3349, 2936, 1642, 1537, 1451, 1258

Example 38

[0102] Trans-4-amino-[(S)-((R)-phenylalanyl) prolyl]aminomethylcyclohexane (compound No. 779 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.69 (br, 3H), 8.09 (br, 4H), 7.37-7.20 (m, 5H), 4.19 (br, 1H), 4.09-4.06 (m, 1H), 3.20-2.82 (m, 5H), 2.0-0.85 (m, 15H)
IR: 3426, 2936, 1649, 1539, 1497, 1454

Example 39

[0103] Trans-4-amino-[(S)-N-((R)-2-ethoxycarbonyloxy-3-phenylpropanoyl) prolyl]aminomethylcyclohexane (compound No. 785 of Table 1) hydrochloride
NMR (DMSO-d^6)
7.78 (m, 3H), 7.30 (m, 5H), 7.15 (d, 1H), 5.22 (t, 1H), 4.20 (m, 1H), 4.08 (m, 3H), 3.64 (m, 1H), 3.02-2.88 (m, 5H), 1.92-1.72 (m, 7H), 1.20-0.94 (m, 9H)
IR: 3397, 2938, 1740, 1655, 1453, 1269

Example 40

[0104] Trans-4-amino-[(S)-N-((R)-2-allylcarbamoyloxy-3-phenylpropanoyl) prolyl]aminomethylcyclohexane (compound No. 787 of Table 1) hydrobromide
NMR (DMSO-d^6)
7.90 (m, 3H), 7.30 (m, 5H), 7.14 (m, 1H), 5.72 (m, 2H), 5.06 (m, 2H), 4.76 (m, 1H), 4.17 (m, 1H), 3.60 (m, 1H), 2.98-2.85 (m, 5H), 1.87-1.70 (m, 7H), 1.23 (m, 7H), 0.90 (m, 2H)
IR: 3364, 2936, 1707, 1645, 1543, 1454, 1256

Example 41

[0105] Trans-4-amino-[(S)-N-((R)-2-hydroxy-2-cyclohexylacetyl) prolyl] aminomethylcyclohexane (compound No. 768 of Table 1) hydrochloride
NMR (DMSO-d^6)
8.21 (br, 3H), 7.95 (m, 1H), 4.53 (m, 1H), 4.18 (d, 1H), 3.95 (m, 1H), 3.07 (m, 3H), 2.18-1.55 (m, 22H), 1.30-1.03 (m, 2H)
IR: 3422, 2928, 2854, 1637, 1450, 1388, 1240, 1114, 1045

Example 42

[0106] Trans-4-amino-[(S)-N-((R)-2-hydroxy-2-phenylacetyl) prolyl] aminomethylcyclohexane (compound No. 783 of Table 1) hydrochloride
NMR (DMSO-d^6)
7.98 (br, 3H), 7.37-7.28 (m, 5H), 5.48 (br, 1H), 5.23 (d, 1H), 4.23 (d, 1H), 3.70-3.35 (m, 2H), 3.0-2.80 (m, 4H), 2.0-1.60 (m, 8H), 1.40-0.90 (m, 5H)
IR: 3329, 2935, 1667, 1626, 1552, 1448

Example 43

[0107] Trans-4-amino-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexane (compound No. 794 of Table 1)
NMR ($CDCl_3$)
7.16 (m, 1H), 5.68 (d, 1H), 4.53 (d, 1H), 4.38 (m, 1H), 4.10 (q, 2H), 4.01 (m, 1H), 3.46-3.07 (m, 4H), 2.30-1.81 (m, 8H), 1.58 (m, 5H), 1.26 (t, 3H), 1.00 (s, 9H), 0.95 (m, 2H)
IR: 3329, 2949, 1642, 1541, 1447, 1248, 1059

[0108] According to the same procedure as that described in Reference Example 1, the following compounds of Examples 44 and 45 were synthesized.

Example 44

[0109] 4-Amidino-[(S)-N-[(R)-2-hydroxy-cyclohexylacetyl] prolyl] aminomethylbenzene (compound No. 82 of Table 1) hydrochloride
NMR (DMSO-d^6)
9.29 (br, 2H), 8.93 (br, 2H), 8.51 (t, 1H), 7.75 (d, 2H), 7.49 (d, 2H), 4.37 (m, 3H), 3.96 (d, 1H), 3.70 (m, 1H), 3.60-3.40 (m, 2H) 2.20-1.0 (m, 14H)

IR: 3227, 2922, 1657, 1607, 1539, 1485, 1458, 1323, 1246, 1032

Example 45

[0110] 4-Amidino-[(S)-N-[(R)-N'-ethoxycarbonylphenylalanyl] prolyl] aminomethylbenzene (compound No.972 of Table 1) hydrochloride
NMR (DMSO-d^6)
9.40 (br, 2H), 9.24 (br, 2H), 8.14 (t, 1H), 7.80 (d, 2H), 7.59 (t, 1H), 7.45 (d, 2H), 7.31-7.15 (m, 5H), 4.50-4.26 (m, 4H), 3.90-3.57 (m, 3H), 3.0-2.7 (m, 3H), 1.9-1.6 (m, 4H), 1.10-1.0 (m, 3H)
IR: 3279, 2364, 1637, 1539, 1491, 1450, 1255, 704

[0111] According to the same procedures as that described in Example 5 the following compounds of Examples 46 to 53 were synthesized.

Example 46

[0112] Trans-4-amidino-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-butyloxy-seryl]prolyl] aminomethylcyclohexane (compound No. 240 of Table 1) hydrochloride
NMR (DMSO-d^6)
8.88 (br, 2H), 8.71 (br, 2H), 7.72 (m, 1H), 6.39 (m, 1H), 4.59 (m, 1H), 4.52 (m, 1H), 4.11 (m, 2H), 3.86-3.71 (m, 2H), 3.58 (m, 2H), 3.22 (m, 2H), 2.79-0.88 (m, 15H), 1.24 (t, 3H), 1.15 (s, 9H)
IR: 3271, 2976, 1685, 1647, 1541, 1448, 1257, 1192, 1095, 1055

Example 47

[0113] Trans-4-amidino-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1',1'-dimethylpropyl)-seryl] prolyl]aminomethylcyclohexane (compound No. 977 of Table 1) hydrochloride
NMR (DMSO-d^6)
8.74 (br, 4H), 7.68 (m, 1H), 6.01 (m, 1H), 4.83 (m, 1H), 4.57 (m, 2H), 3.74 (m, 2H), 3.50 (m, 2H), 3.14 (m, 1H), 2.97 (m, 1H), 2.5-0.9 (m, 16H), 1.24 (dd, 6H), 1.09 (s, 6H), 0.81 (t, 3H)
IR: 3314, 2978, 1693, 1641, 1543, 1450, 1375, 1261, 1111, 1059

Example 48

[0114] Trans-4-amidino-[(S)-N-[(R)-N'-ethoxycarbonyl-O-(1',1'-dimethylpropyl)-seryl] prolyl]aminomethylcyclohexane (compound No. 978 of Table 1) hydrochloride
NMR (DMSO-d^6)
8.75 (br, 4H), 7.55 (m, 1H), 6.40 (m, 1H), 4.52 (m, 2H), 4.13 (m, 2H), 3.88-3.70 (m, 2H), 3.55 (m, 2H), 3.28 (m, 1H), 2.87-2.70 (m, 1H), 2.20-1.20 (m, 14H), 1.27 (t, 3H), 1.09 (s, 6H), 0.81 (t, 3H), 1.10-0.90 (m, 2H)
IR: 3292, 2974, 1689, 1645, 1543, 1448, 1259, 1095, 1055

Example 49

[0115] Trans-4-amidino-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1'-ethyl-1'-methyl-propyl)-seryl] prolyl]aminomethylcyclohexane (compound No. 979 of Table 1) hydrochloride
NMR (DMSO-d^6)
8.78 (s, 2H), 8.69 (s, 2H), 7.55 (br, 1H), 5.99 (br, 1H), 4.84 (m, 1H), 4.54 (m, 2H), 3.71 (m, 2H), 3.49 (m, 2H), 3.20-0.90 (m, 16H), 1.64 (q, 4H), 1.23 (t, 6H), 1.03 (s, 3H), 0.78 (t, 6H)
IR: 3315, 2976, 2934, 1685, 1641, 1543, 1450, 1375, 1261, 1111

Example 50

[0116] Trans-4-amidino-[(S)-N-[(R)-N'-ethoxycarbonyl-S-t-butyl-cystinyl]prolyl] aminomethylcyclohexane (compound No. 980 of Table 1) hydrochloride
NMR (DMSO-d^6)
8.82 (br, 2H), 8.74 (br, 2H), 7.47 (m, 1H), 6.63 (m, 1H), 4.60-4.40 (m, 2H), 4.20-4.21 (m, 2H), 4.00 (m, 1H), 3.72 (m, 1H), 3.24 (m, 1H), 2.87 (m, 2H), 2.65 (m, 1H), 2.18-1.31 (m, 12H), 1.31 (s, 9H), 1.27 (t, 3H), 1.10-0.90 (m, 2H)
IR: 3298, 2932, 1693, 1641, 1541, 1448, 1304, 1257, 1161, 1047

Example 51

[0117] Trans-4-amidino-[(S)-N-[(R)-N'-isopropoxycarbonyl-0-(1'-methylcyclopentyl)-seryl] prolyl]aminomethylcyclohexane (compound No. 981 of Table 1) hydrochloride
NMR (DMSO-d^6)
8.79 (br, 4H), 7.64 (m, 1H), 5.97 (m, 1H), 4.83 (m, 1H), 4.55 (m, 2H), 3.76 (m, 2H), 3.52 (m, 2H), 3.15-1.20 (m, 22H), 1.27-1.13 (m, 9H), 1.13-0.95 (m, 2H)
IR: 3329, 2934, 1684, 1639, 1541, 1450, 1261, 1182, 1111, 1060, 918

Example 52

[0118] Trans-4-amidino-[(S)-N-[(R)-N'-isopropoxycarbonyl-0-t-butyl-threonyl] prolyl]aminomethylcyclohexane (compound No. 982 of Table 1) hydrochloride
NMR (DMSO-d^6)
8.74 (m, 4H), 7.80 (m, 1H), 5.66 (m, 1H), 4.85 (m, 1H), 4.57 (m, 1H), 4.29 (m, 1H), 3.80-3.60 (m, 3H), 3.05 (m, 2H), 2.60 (m, 1H), 2.50-1.20 (m, 1H), 1.27-1.22 (m, 15H), 1.15 (d, 3H), 1.10-0.90 (m, 2H)
IR: 3331, 2978, 1697, 1639, 1543, 1450, 1375, 1265, 1182, 1111

Example 53

[0119] Trans-4-amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-3-isopropylthio-3-methyl-butanoyl] prolyl]aminomethylcyclohexane (compound No. 983 of Table 1) hydrochloride
NMR (DMSO-d^6)
9.13 (br, 2H), 8.46 (br, 2H), 7.30 (m, 1H), 5.85 (m, 1H), 4.55 (m, 1H), 4.36 (m, 1H), 4.15-3.85 (m, 3H), 3.69 (m, 1H), 3.02 (m, 2H), 2.30 (m, 1H), 2.00-1.20 (m, 13H), 1.48 (s, 3H), 1.33 (s, 3H), 1.30-1.20 (m, 9H), 1.05-0.85 (m, 2H)
IR: 3420, 2974, 1635, 1556, 1521, 1448, 1385, 1298, 1259, 1060

[0120] According to the same procedures as that described in Example 11, the following compounds of Examples 54 to 80 were synthesized.

Example 54

[0121] 4-[(S)-N-[(R)-2-hydroxy-cyclohexylacetyl] prolyl] aminomethylbenzamidoxime (compound No. 391 of Table 1)
NMR (DMSO-d^6)
9.55 (br, 1H), 8.31 (t, 1H), 7.59 (d, 2H), 7.24 (d, 2H), 5.73 (br, 2H), 4.57 (m, 1H), 4.26-4.32 (m, 3H), 3.91 (br, 1H), 3.40-3.60 (m, 2H), 2.05-0.80 (m, 15H)
IR: 3375, 2926, 2853, 1638, 1561, 1451, 1385, 1244

Example 55

[0122] 4-[(S)-N-[(R)-N'-isopropoxycarbonyl-phenylalanyl] prolyl] aminomethylbenzamidoxime (compound No. 395 of Table 1)
NMR ($CDCl_3$)
7.65 (br, 1H), 7.53 (d, 2H), 7.29-7.19 (m, 8H), 5.89 (d, 2H), 5.01 (br, 2H), 4.58-4.45 (m, 4H), 4.27 (dd, 1H), 3.65 (br, 1H), 3.10-2.93 (m, 2H), 2.58 (q, 1H), 2.17 (br, 1H), 1.90-1.50 (m, 2H), 1.11 (d, 4H), 0.96 (d, 2H)
IR: 3331, 2980, 2880, 2365, 1639, 1539, 1452, 126

Example 56

[0123] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-phenylacetyl] prolyl] aminomethylbenzamidoxime (compound No. 403 of Table 1)
NMR ($CDCl_3$)
7.80 (br, 1H), 7.47 (d, 2H), 7.40-7.14 (m, 8H), 6.11 (dd, 1H), 5.43 (dd, 1H), 4.98 (br, 2H), 4.70-4.54 (m, 2H), 4.50-4.20 (m, 1H), 4.15-4.00 (m, 1H), 4.00-3.80 (m, 2H), 3.25-3.19 (m, 1H), 2.30-1.80 (m, 4H), 1.16 (dt, 3H)
IR: 3339, 2980, 2365, 1641, 1524, 1437, 1385, 1057

Example 57

[0124] 4-[(S)-N-[(R)-N'-ethoxycarbonyl-valyl]prolyl] aminomethylbenzamidoxime (compound No. 407 of Table 1)

NMR ($CDCl_3$)
7.57 (br, 1H), 7.54 (d, 2H), 7.20 (d, 2H), 5.98 (d, 1H), 4.97 (br, 2H), 4.68-4.59 (m, 2H), 4.24 (dd, 1H), 4.07 (t, 1H), 4.10-4.00 (m, 1H), 3.90-3.80 (m, 1H), 3.60-3.45 (m, 2H), 2.31 (br, 1H), 2.20-1.95 (m, 4H) 1.88 (d, 1H), 1.01 (t, 3H), 0.97 (d, 6H)
IR: 3337, 2971, 2878, 2363, 1640, 1539, 1445, 1277, 1238

Example 58

[0125] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-3,3-dimethylbutanoyl] prolyl] aminomethylbenzamidoxime (compound No. 409 of Table 1)
NMR (DMSO-d^6)
8.01 (br, 1H), 7.59 (d, 2H), 7.21 (d, 2H), 7.19-7.15 (m, 1H), 5.73 (br, 2H), 4.36-4.24 (m, 4H), 4.0-3.60 (m, 4H), 2.10-1.80 (m, 5H), 1.06 (t, 3H), 0.96 (s, 9H)
IR: 3345, 2966, 2364, 1647, 1535, 1443, 1240

Example 59

[0126] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-heptanoyl) prolyl] aminomethylbenzamidoxime (compound No. 411 of Table 1)
NMR ($CDCl_3$)
7.63 (m, 1H), 7.51 (d, 2H), 7.20 (d, 2H), 5.85 (d, 2H), 4.99 (br, 1H), 4.67-4.58 (m, 2H), 4.35-4.28 (m, 2H), 3.99 (br, 1H), 3.86-3.80 (m, 1H), 3.58-3.50 (m, 2H), 2.31 (br, 1H), 2.07-1.90 (m, 3H), 1.80-1.50 (m, 2H), 1.40-1.10 (m, 5H), 1.03 (t, 3H), 1.01-0.84 (m, 3H)
IR: 3347, 2961, 2363, 2342, 1641, 1541, 1447, 1263, 1049

Example 60

[0127] 4-[(S)-N-[(R)-2-t-butyloxycarbonylamino-heptanoyl] prolyl] aminomethylbenzamidoxime (compound No. 412 of Table 1)
NMR ($CDCl_3$)
7.74-7.70 (m, 1H), 7.49 (d, 2H), 7.27 (t, 1H), 7.20 (d, 2H), 5.43 (d, 1H), 4.93 (br, 2H), 4.65 (d, 1H), 4.48-4.25 (m, 3H), 3.93 (br, 1H), 3.50 (q, 1H), 2.40-2.30 (m, 1H), 2.10-1.90 (m, 3H), 1.70-1.50 (m, 2H), 1.42-1.21 (m, 13H), 0.92-0.80 (m, 3H)
IR: 3337, 2961, 2934, 2363, 1641, 1535, 1449, 1368, 1165

Example 61

[0128] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl] prolyl] aminomethylbenzamidoxime (compound No. 418 of Table 1)
NMR ($CDCl_3$)
7.58-7.51 (m, 1H), 7.53 (d, 2H), 7.20 (d, 2H), 5.87 (d, 1H), 5.01 (br, 2H), 4.64-4.56 (m, 2H), 4.40 (q, 1H), 4.26 (dd, 1H), 4.10-4.00 (m, 1H), 3.84-3.78 (m, 1H), 3.53-3.47 (m, 2H), 2.32 (br, 1H), 2.10-1.90 (m, 3H), 1.61 (d, 2H), 1.00 (t, 3H), 0.97 (s, 9H)
IR: 3324, 2957, 2263, 2342, 1642, 1541, 1445, 1248, 1059

Example 62

[0129] 4-[(S)-N-[(R)-N'-(ethoxycarbonylmethyl)oxycarbonyl-phenylalanyl] prolyl]aminomethylbenzamidoxime (compound No. 984 of Table 1)
NMR ($CDCl_3$)
7.54 (d, 2H), 7.41 (br, 1H), 7.28-7.20 (m, 8H), 6.70 (d, 1H), 5.09 (br, 2H), 4.66 (dd, 1H), 4.60-4.55 (m, 2H), 4.22-4.00 (m, 4H), 4.03 (q, 2H), 3.62 (br, 1H), 3.10-3.02 (m, 2H), 2.60-2.40 (m, 1H), 2.14 (br, 1H), 2.00-1.50 (m, 3H), 1.22 (t, 3H)
IR: 3356, 3063, 2980, 2364, 1717, 1641, 1539, 1451, 1213, 702

Example 63

[0130] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-cyclohexylacetyl] prolyl] aminomethylbenzamidoxime (compound No.

985 of Table 1)
NMR ($CDCl_3$)
7.52 (d, 2H), 7.54-7.50 (m, 1H), 7.20 (d, 2H), 6.03 (br, 1H), 4.97 (br, 2H), 4.68 (q, 2H), 4.22 (dd, 1H), 4.12-4.03 (m, 2H), 3.64-3.47 (m, 1H), 3.20 (s, 3H), 2.32 (br, 1H), 2.05-1.60 (m, 9H), 1.28-0.97 (m, 6H)
IR: 3343, 2928, 2853, 2365, 1639, 1541, 1449, 1260

Example 64

[0131] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-2'-thienylacetyl] prolyl] aminomethylbenzamidoxime (compound No. 986 of Table 1)
NMR ($CDCl_3$)
7.80-7.60 (m, 1H), 7.46 (dd, 2H), 7.40-6.95 (m, 5H), 6.13 (dd, 1H), 5.71 (dd, 1H), 4.99 (br, 2H), 4.75-4.20 (m, 3H), 4.00-3.80 (m, 2H), 3.70-3.50 (m, 1H),3.40-3.30 (m, 1H), 2.40-1.80 (m, 4H), 1.16 (dt, 3H)
IR: 3337, 2978, 2364, 1641, 1524, 1443, 1240, 1057, 710

Example 65

[0132] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-4'-fluorophenylacetyl] prolyl] aminomethylbenzamidoxime (compound No. 987 of Table 1)
NMR ($CDCl_3$)
7.80 (t, 1H), 7.46-7.27 (m, 4H), 7.19-6.92 (m, 4H), 6.19-6.15 (m, 1H), 5.50 (dd, 1H), 5.02 (br, 2H), 4.70-4.20 (m, 3H), 4.10-3.70 (m, 4H), 3.22-3.15 (m, 1H), 2.25-1.80 (m, 4H), 1.16 (dt, 3H)
IR: 3345, 3073, 2980, 2363, 2344, 1641, 1510, 1143

Example 66

[0133] 4-[(S)-N-[(R)-N'-benzyloxycarbonyl-phenylalanyl] prolyl] aminomethylbenzamidoxime (compound No. 988 of Table 1)
NMR ($CDCl_3$)
7.50 (d, 2H), 7.49-7.30 (m, 1H), 7.26-7.12 (m, 12H), 6.40-6.10 (m, 1H), 4.85 (br, 2H), 4.90-4.70 (m, 1H), 4.55-4.40 (m, 4H), 4.30-4.20 (m, 1H), 3.70-3.60 (m, 1H), 3.03-2.95 (m, 1H), 2.20-2.15 (m, 1H), 2.00-1.45 (m, 3H)

Example 67

[0134] 4-[(S)-N-(R)-2-t-butyloxycarbonylamino-4,4-dimethylpentanoyl] prolyl] aminomethylbenzamidoxime (compound No. 989 of Table 1)
NMR ($CDCl_3$)
7.67 (t, 1H), 7.53 (d, 2H), 7.22 (d, 2H), 5.34 (d, 1H), 4.91 (br, 2H), 4.65 (d, 1H), 4.42-4.34 (m, 3H), 4.00-3.90 (m, 1H), 3.48 (q, 1H), 2.40-2.30 (m, 1H), 2.02-1.95 (m, 3H), 1.56-1.53 (m, 2H), 1.31 (s, 9H), 0.98 (s, 9H)
IR: 3345, 2959, 2367, 1641, 1535, 1446, 1367, 1167

Example 68

[0135] 4-[(S)-N-[(R)-N'-dimethylcarbamoyl-phenylalanyl] prolyl] aminomethylbenzamidoxime (compound No. 990 of Table 1)
NMR (DMSO-d^6)
9.56 (s, 1H), 8.11 (t, 1H), 7.56 (d, 2H), 7.18 (d, 2H), 7.29-7.16 (m, 5H), 6.70 (d, 1H), 5.74 (br, 2H), 4.40-4.05 (m, 4H), 2.94 (d, 2H), 2.93-2.70 (m, 2H), 2.60 (s, 6H), 1.90-1.60 (m, 4H)
IR: 3306, 2932, 2880, 2363, 2341, 1634, 1541, 1453

Example 69

[0136] 4-[(S)-N-[(S)-N'-benzyloxycarbonyl-β-t-butylaspartyl] prolyl] aminomethylbenzamidoxime (compound No. 991 of Table 1)
NMR ($CDCl_3$)
7.63 (br, 1H), 7.51 (d, 2H), 7.33-7.26 (m, 5H), 7.18 (d, 2H), 6.07 (d, 1H), 5.08 (dd, 2H), 4.92 (br, 2H), 4.90-4.70 (m, 1H), 4.66 (d, 1H), 4.40 (d, 2H), 3.90-3.80 (m, 2H), 3.0-2.90 (m, 1H), 2.55 (dd, 1H), 2.35-2.20 (m, 1H), 2.08-1.90 (m, 3H), 1.25 (s, 9H)

IR: 3364, 3063, 2978, 2363, 2343, 2343, 1717, 1641, 1539, 1450, 1369, 1253 1157

Example 70

[0137] Trans-4-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-butoxy-seryl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 485 of Table 1)
NMR ($CDCl_3$)
7.16 (m, 1H), 5.53 (m, 1H), 4.60-4.53 (m, 2H), 4.47 (s, 2H), 4.13-4.06 (m, 2H), 3.76 (br, 2H), 3.60-3.50 (m, 2H), 3.07 (br, 2H), 2.41 (m, 2H), 2.04-1.20 (m, 12H), 1.27 (t, 3H), 1.16 (s, 9H), 1.03-0.94 (m, 2H)
IR: 3352, 2930, 1701, 1651, 1541, 1448, 1259, 1053, 754

Example 71

[0138] Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-t-butylseryl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 486 of Table 1)
NMR ($CDCl_3$)
7.19 (m, 1H), 5.40 (d, 1H), 4.87 (m, 1H), 4.61-4..53 (m, 2H), 4.47 (br, 2H), 3.75 (m, 2H), 3.60-3.40 (m, 2H), 3.08 (t, 2H), 2.40 (m, 1H), 2.20-1.20 (m, 12H), 1.21 (dd, 6H), 1.19 (s, 9H), 1.10-0.90 (m, 2H)
IR: 3356, 2976, 1697, 1649, 1541, 1448, 1261, 1190, 1109, 1022

Example 72

[0139] Trans-4-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-(1',1'-dimethylpropyl]-seryl)prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 487 of Table 1)
NMR ($CDCl_3$)
7.14 (m, 1H), 5.51 (d, 1H), 4.60-4.50 (m, 2H), 4.48 (br, 2H), 4.09 (m, 2H), 3.78 (m, 2H), 3.55-3.45 (m, 2H), 3.06 (m, 2H), 2.35 (m, 1H), 2.20-0.90 (m, 16H), 1.24 (t, 3H), 1.10 (s, 6H), 0.82 (t, 3H)
IR: 3346, 2976, 2930, 1649, 1543, 1448, 1261, 1176, 1095, 1055

Example 73

[0140] Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1',1'-dimethylpropyl)-seryl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 488 of Table 1)
NMR ($CDCl_3$)
7.18 (m, 1H), 5.38 (d, 1H), 4.86 (m, 1H), 4.61-4.50 (m, 2H), 4.47 (br, 2H), 3.77 (m, 2H), 3.57-3.42 (m, 2H), 3.06 (t, 2H), 2.39 (m, 1H), 2.20-0.90 (m, 16H), 1.23 (dd, 6H), 1.10 (s, 6H), 0.82 (t, 3H)
IR: 3346, 2976, 1703, 1651, 1541, 1448, 1263, 1178, 1109, 1030

Example 74

[0141] Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1'-ethyl-1'-methyl-propyl)-seryl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 490 of Table 1)
NMR ($CDCl_3$)
7.17 (br, 1H), 5.35 (br, 1H), 4.86 (m, 1H), 4.60-4.50 (m, 2H), 4.47 (br, 2H), 3.78 (m, 2H), 3.53-3.38 (m, 2H), 3.07 (t, 2H), 2.37-1.20 (m, 17H), 1.23 (t, 6H), 1.06 (s, 3H), 1.06-0.82 (m, 2H), 0.79 (t, 6H)
IR: 3350, 2976, 2932, 1651, 1541, 1450, 1375, 1263, 1109, 1026

Example 75

[0142] Trans-4-[(S)-N-[(R)-N'-ethoxycarbonyl-S-t-butyl-cystinyl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 492 of Table 1)
NMR ($CDCl_3$)
7.27 (m, 1H), 5.81 (m, 1H), 4.60-4.40 (m, 2H), 4.88 (br, 2H), 4.11 (m, 2H), 3.87 (m, 1H), 3.68 (m, 1H), 3.06 (m, 2H), 2.90-2.70 (m, 2H), 2.37 (m, 1H), 2.10-1.20 (m, 12H), 1.32 (s, 9H), 1.25 (t, 3H), 1.10-0.90 (m, 2H)
IR: 3346, 2930, 1699, 1649, 1541, 1448, 1257, 1163, 1051, 929

Example 76

[0143] Trans-4-[(S)-N-[(R)-2-ethoxycarbonylamino-3-isopropylthio-3-methylbutanoyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 497 of Table 1)
NMR ($CDCl_3$)
7.16 (m, 1H), 5.62 (m, 1H), 4.61 (d, 1H), 4.47 (br, 2H), 4.35 (d, 1H), 4.12 (m, 2H), 3.96 (m, 1H), 3.76 (m, 1H), 3.10 (m, 1H), 3.00 (m, 2H), 2.38 (m, 1H), 2.00-1.20 (m, 12H), 1.47 (s, 3H), 1.40 (s, 3H), 1.33-1.25 (m, 9H), 1.00-0.90 (m, 2H)
IR: 3354, 2928, 1653, 1541, 1446, 1367, 1302, 1251, 1155, 1055

Example 77

[0144] Trans-4-[(S)-N-[(S)-N'-t-butyloxycarbonyl-seryl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 992 of Table 1)
NMR ($CDCl_3$)
7.76 (br, 1H), 6.10 (br, 1H), 5.40 (br, 1H), 4.60 (br, 4H), 3.96 (br, 4H), 3.16-1.21 (m, 15H), 1.40 (s, 9H), 0.99 (br, 2H)
IR: 3314, 2978, 1691, 1639, 1541, 1450, 1367, 1165, 1049

Example 78

[0145] Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-t-butyl-threonyl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 993 of Table 1)
NMR ($CDCl_3$)
7.24 (m, 1H), 5.43 (d, 1H), 4.85 (m, 1H), 4.57 (d, 1H), 4.47 (br, 2H), 4.23 (t, 1H), 3.92 (t, 1H), 3.80-3.70 (m, 2H), 3.06 (m, 2H), 2.36 (m, 1H), 2.00-1.20 (m, 12H), 1.23 (s, 9H) 1.23 (dd, 6H), 1.15 (d, 3H), 1.10-0.90 (m, 2H)
IR: 3354, 2978, 1699, 1649, 1543, 1448, 1373, 1257, 1192, 1111, 1032

Example 79

[0146] Trans-4-[(S)-N-[(R)-2-acetoxy-cyclohexylacetyl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 994 of Table 1)
NMR ($CDCl_3$)
6.80 (br, 1H), 4.61 (t, 2H), 4.49 (br, 2H), 3.90-3.84 (m, 1H), 3.51-3.40 (m, 1H), 3.10-2.85 (m, 2H), 2.38 (br, 1H), 2.11 (s, 3H), 2.06-0.80 (m, 25H)
IR: 3484, 3389, 2928, 2855, 1725, 1649, 1451, 1250

Example 80

[0147] Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1'-methylcyclopentyl)-seryl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 995 of Table 1)
NMR ($CDCl_3$)
7.18 (m, 1H), 5.42 (m, 1H), 4.85 (m, 2H), 4.60-4.49 (m, 4H), 3.73 (m, 2H), 3.57-3.42 (m, 2H), 3.08 (m, 1H), 2.40 (m, 1H), 2.04-1.20 (m, 21H), 1.27-1.20 (m, 9H), 1.03-0.94 (m, 2H)
IR: 3356, 2932, 1695, 1653, 1541, 1448, 1263, 1111, 1030, 918

[0148] According to the same procedures as that described in Reference Example 2, the following compound of Example 81 was synthesized.

Example 81

[0149] Trans-4-amino-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-butyloxy-seryl] prolyl] aminomethylcyclohexane (compound No. 1003 of Table 1) hydrochloride
NMR (DMSO-d^6)
8.29 (s, 3H), 7.20 (s, 1H), 5.69 (d, 1H), 4.58-4.47 (m, 2H), 4.12 (m, 2H), 3.82 (m, 1H), 3.61-3.48 (m, 2H), 3.09 (m, 2H), 2.32-0.86 (m, 15H), 1.27 (t, 3H), 1.16 (s, 9H)
IR: 3358, 2974, 1645, 1541, 1448, 1257, 1192, 1053

[0150] According to the same procedures as that described in Example 67, the following compounds 126 to 130 were synthesized.

Experimental Example 1: Determination of antithrombin activity

(i) The measuring method for hydrolysis inhibition of synthetic substrate (S-2238)

[0151] S-2238 (manufactured by Kabi Co.) is dissolved in a Tris hydrochloric acid buffer solution (pH: 8.3) to prepare a S-2238-0.4 M Tris hydrochloric acid solution having a concentration of 80 μm. To 175 μl of the solution, an aqueous solution of a compound of the present invention (515 μl) is added. After incubating at 37°C for one minute, 10 μl of a bovine thrombin solution (4.4 units/ml, manufactured by Mochida Co., Ltd.) is added. A hydrolysis reaction rate of the substrate is determined by measuring a change in absorbance of 405 nm at 37°C.

[0152] The inhibitor concentration exhibiting an absorbance which is half as large as that obtained in case of adding no inhibitor (compound of the present invention) was determined as IC_{50} (μm).

(ii) The measuring method for coagulation inhibition of rat plasma

[0153] The compound of the present invention is dissolved in water or saline to form a solution of a total volume of 0.1 ml. To the solution, 0.1 ml of rat plasma is added and the mixture is incubated at 37°C for 30 seconds. Then, 0.1 ml of bovine thrombin (8 units/ml, Mochida Co., Ltd.) is added and the coagulation time is measured at 37°C. The concentration of the inhibitor (i.e., the compound of the present invention) which doubles the coagulation time that obtained in the absence of the inhibitor was determined as IC_{50} (μm).

(iii) The measuring method for antithrombin activity of rat plasma on oral administration

[0154] To a rat abstained from bait overnight, an aqueous solution or suspension of the present compound (inhibitor) (30 mg/kg) is orally administered using an oral sound.

[0155] After one hour, 2 ml of blood is collected from cava abdominalis and the antithrombin activity in plasma is measured using a method of the above item (ii). As a control experiment, the coagulation time of blood collected from a rat which has not been administered the inhibitor was measured. The extension effect on the coagulation time is represented by the numerical value obtained by comparing the data with those obtained in control experiment, wherein the numerical value obtained in the control experiment was assumed to be 1.

Experimental Example 2: Determination of Antitrypsin activity

(i) The measuring method for hydrolysis inhibition of synthetic substrate (S-2222)

[0156] S-2222 (manufactured by Kabi Co.) is dissolved in a Tris hydrochloric acid (pH: 8.3) to prepare a S-2222-0.4M Tris hydrochloric acid solution having a concentration of 400 μm. To the solution (175 μl), 515 μl of a solution of a compound of the present invention is added. After incubating at 37°C for one minute, 10 μl of a bovine trypsin solution (1 to 2 mg/ml, manufactured by Sigma Co.) is added. A hydrolysis reaction rate of the substrate is determined by measuring a change in absorbance of 405 nm at 37°C.

[0157] The inhibitor concentration exhibiting an absorbance which is half as large as that obtained in case of adding no inhibitor (compound of the present invention) was determined as IC_{50} (μm).

[0158] The results are shown in Table 2.

Table 2

	Antithrombin activity IC_{50} (μm)			
Example No.	Synthetic substrate method	Rat plasma method	Antitrypsin activity IC_{50} (μm)	Thrombin coagulation time extension coagulation on oral administration
Ref 1				
1		0.056		3.16
3	0.72	0.59		
5	0.011	0.038	2.2	
6	0.021		1.7	

Table 2 (continued)

	Antithrombin activity IC_{50} (μm)			
Example No.	Synthetic substrate method	Rat plasma method	Antitrypsin activity IC_{50} (μm)	Thrombin coagulation time extension coagulation on oral administration
Ref 1				
7	0.015	0.053	3.2	
8	0.021		1.0	
9	0.014		0.94	
10	0.017	0.058	3.6	
11				3.28
12		> 300		2.82
13				4.16
14				3.52
15				4.35
17				2.75
18				2.77
19				3.58
20				3.99
22				3.72
23				2.85
24				4.37
26				2.37
27				2.70
28				2.94
29				4.36
30				3.09
33				2.16
34				2.34
Ref 2				
	0.13	0.045	14	4.10
36	0.13	0.080	14	2.10
37		0.082		
38		0.097		2.35
41		0.056		
42		0.088		2.18
43		0.13		1.25

Experimental Example 3: Acute toxicity test

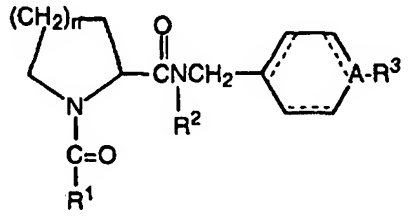
[0159] Acute toxicity was determined in rat. An approximate lethal dose was determined by conducting an oral acute toxicity test using rats. The results are shown in Table 3.

Table 3

	Approximate lethal dose mg/kg	
	Male	Female
Example No.		
Ref 2	Not less than 2000	Not less than 2000
20	Not less than 2000	Not less than 2000
24	Not less than 2000	Not less than 2000

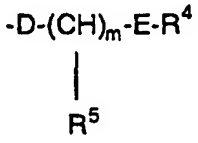
Claims

1. A prolineamide derivative represented by the formula (I):



(I)

wherein A is a carbon atom or a nitrogen atom;
n is an integer of 0 to 2;
a broken line is no bond or a single bond;
R^1 is



{wherein D and E independently indicate a single bond or an optionally branched C_1-C_6 alkylene group;

R^4 is a C_1-C_6 alkyl group; -OR^6 (R^6 is a hydrogen atom, a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyl group), -SR^7 (R^7 is a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyl group), -SOR^8 (R^8 is an optionally substituted C_6-C_{10} aryl group or an optionally substituted C_3-C_8 cycloalkyl group), -SO_2R^9 (R^9 is an optionally substituted C_6-C_{10} aryl group or an optionally substituted C_3-C_8 cycloalkyl group), -COR^{10} (R^{10} is a hydroxyl group, a C_1-C_6 alkoxy group, an optionally substituted C_6-C_{10} aryl group or an optionally substituted C_3-C_8 cycloalkyl group), -NHR^{11} (R^{11} is a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyl group), -$NHCOR^{12}$ (R^{12} is a C_1-C_6 alkoxy group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyloxy group), -$NHSO_2R^{13}$ (R^{13} is a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group, an optionally substituted C_7-C_{12} aralkyl group, or an optionally substituted 5- to 10-membered heterocyclic group), an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group, an optionally substituted 5- to 10-membered heterocyclic group or -$SiR^{14}R^{15}R^{16}$ (R^{14}, R^{15}, and R^{16} independently indicate a C_1-C_6 alkyl group);

R^5 is a -OR^{17} (R^{17} is a hydrogen atom, -$SiR^{22}R^{23}R^{24}$ (R^{22}, R^{23}, and R^{24} independently indicate a C_1-C_6 alkyl group), a C_1-C_6 alkyl group, or an optionally substituted 5- to 10-membered heterocyclic group)), -$OCOR^{18}$ (R^{18}

is a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, an amino group, a C_1-C_6 alkylamino group, a C_2-C_{12} dialkylamino group or a C_2-C_7 alkenylamino group), -NHR^{19} (R^{19} is a hydrogen atom, a C_1-C_6 alkyl group or an optionally substituted C_7-C_{12} aralkyl group), -$NHCOR^{20}$ (R^{20} is a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_6 haloalkyl group, a C_1-C_6 alkoxy group, an optionally substituted C_3-C_8 cycloalkyl group, a C_2-C_7 carboxyalkyloxy group, a C_2-C_7 alkenyloxy group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_6-C_{10} aryloxy group, a C_3-C_9 alkoxycarbonylalkoxy group, a C_2-C_{12} dialkylamino group or an optionally substituted C_7-C_{12} aralkyloxy group) or -$NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group, a C_1-C_6 haloalkyl group, a C_2-C_7 carboxyalkyl group, an optionally substituted C_6-C_{10} aryl group, a C_3-C_9 alkoxycarbonylalkyl group or an optionally substituted C_7-C_{12} aralkyl group); and m is 0 or 1 ;

each of said 5- to 10-membered heterocyclic groups is independently selected from a furan ring, a tetrahydrofuran ring, a pyran ring, a benzofuran ring, a chroman ring, a thiophene ring, a benzothiophene ring, a pyrrole ring, an imidazole ring, a pyrazole ring, a triazole ring, a pyridine ring, a piperidine ring, a pyrazine ring, a piperazine ring, a pyrimidine ring, an indole ring, a benzimidazole ring, a purine ring, a quinoline ring, a phthalazine ring, a quinazoline ring, a cinnoline ring, an oxazole ring, a thiazole ring and a morpholine ring;

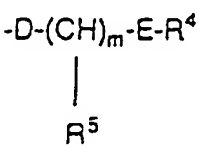
each of said optional substituents being independently selected from C_1-C_6 alkyl group, a C_1-C_6 haloalkyl group, a C_1-C_6 alkoxy group, a hydroxyl group, a carboxyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 carboxyalkyloxy group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkoxycarbonyloxy group, a C_8-C_{13} aralkyloxycarbonyl group, a C_3-C_9 alkoxycarboxyalkoxy group and a halogen atom};

R^2 is a hydrogen atom or a C_1-C_6 alkyl group; and R^3 is -$C(=NR^{25})NH_2$ (wherein R^{25} is a hydrogen atom or a hydroxyl group) or -NH_2; provided that R^3 is -$C(=NR^{25})NH_2$ (R^{25} is as defined above) when A is a nitrogen atom, or a salt or hydrate thereof;

with the proviso that if the substituent R^2 represents a hydrogen atom, the group "D" represents a single bond, and the index n is 1 or 2, then neither of the substituents R^4 or R^5 represents a group including an aminosulfonyl moiety.

2. A compound according to Claim 1, wherein A is a carbon atom.

3. A compound according to Claim 1 or Claim 2, wherein n is 1 or 2; R^1 is



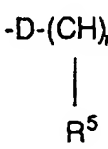
{wherein D and E independently indicate a single bond or an optionally branched C_1-C_6 alkylene group;

R^4 is a C_1-C_6 alkyl group; -OR^6 (R^6 is a C_1-C_6 alkyl group; a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; or a C_7-C_{12} aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group); -SR^7 (R^7 is a C_1-C_6 alkyl group; a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; or a C_7-C_{12} aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group); -COOH; a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; a C_3-C_8 cycloalkyl group; or -$SiR^{14}R^{15}R^{16}$ (R^{14}, R^{15}, and R^{16} independently indicate a C_1-C_6 alkyl group);

R^5 is -OH, -$OCOR^{18}$ (R^{18} is a C_1-C_6 alkoxy group or a C_2-C_7 alkenylamino group), -NH_2, -$NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group, a C_6-C_{10} aryloxy group, a C_3-C_9 alkoxycarbonylalkoxy group, a C_2-C_{12} dialkylamino group or a C_7-C_{12} aralkyloxy group) or -$NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group, a C_2-C_7 carboxyalkyl group, a C_6-C_{10} aryl group, a C_3-C_9 alkoxycarbonylalkyl group or a C_7-C_{12} aralkyl group); and m is 0 or 1}; and

R^2 is a hydrogen atom.

4. A compound according to Claim 1 or Claim 2, wherein n is 1; R^1 is



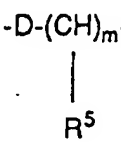
{wherein D and E independently indicate a single bond or an optionally branched C_1-C_6 alkylene group;

R^4 is a C_1-C_6 alkyl group; -OR^6 (R^6 is a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group or C_7-C_{12} aralkyl group); -SR^7 (R^7 is a C_1-C_6 alkyl group); a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group; or a C_3-C_6 cycloalkyl group;

R^5 is -OH, NH_2, -$NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group or a C_7-C_{12} aralkyloxy group) or -$NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group or a C_6-C_{10} aryl group); and m is 1}; and

R^2 is a hydrogen atom,

5. A compound according to Claim 1 or Claim 2, wherein n is 1; R^1 is



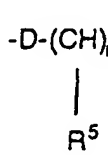
{wherein D is a single bond; E is a single bond or a C_1-C_6 alkylene group;

R^4 is a C_1-C_6 alkyl group; -OR^6 (R^6 is a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group or C_7-C_{12} aralkyl group); -SR^7 (R^7 is a C_1-C_6 alkyl group); a C_6-C_{10} aryl group which may be substituted with at least one or more substituents selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group; or a C_3-C_6 cycloalkyl group;

R^5 is -NH_2, -$NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group or a C_7-C_{12} aralkyloxy group) or -$NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group or a C_6-C_{10} aryl group); and m is 1}; and

R^2 is a hydrogen atom.

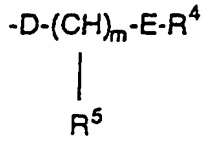
6. A compound according to claim 1, wherein A is a carbon atom; n is 1; R^1 is



{wherein D is a single bond; E is a single bond or a C_1-C_3 alkylene group; R^4 is a C_3-C_6 alkyl group),-OR^6 (R^6 is

a C_1-C_6 alkyl group, a phenyl group, or a C_3-C_6 cycloalkyl group; R^5 is -OH,-NHR^{19} (R^{19} is a hydrogen atom), -$NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group) or -$NHSO_2R^{21}$ (R^{21} is a C_1-C_3 alkyl group); and m is 1}; and
R^2 is a hydrogen atom.

7. A compound according to Claim 1 or Claim 2, wherein n is 1; R^1 is



{D is a single bond; E is a single bond or a C_1-C_6 alkylene group; R^4 is a C_1-C_6 alkyl group; R^5 is -$NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group); and m is 1};
R^2 is a hydrogen atom; and
R^3 is -$C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom or a hydroxyl group).

8. Trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl) prolyl]aminomethylcyclohexanecarboxamidoxime or a salt or hydrate thereof.

9. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 8 and a pharmaceutically acceptable carrier therefor.

10. The use of a compound as claimed in any one of claims 1 to 8 in the manufacture of a medicament effective as a protease inhibitor.

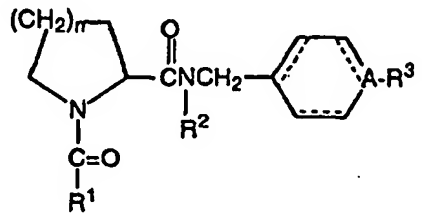
11. A compound according to any of claims 1-8 for use as a medicament.

12. Use of a compound according co any of claims 1-8 for the manufacture of an anti-coagulant medicament.

13. Use of a compound according to any of claims 1-8 for the manufacture of a medicament for the treatment of pancreatitis.

Patentansprüche

1. Prolinamidderivat, dargestellt durch die Formel (I):



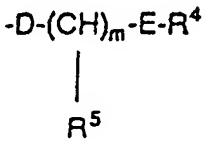
(I)

wobei A ein Kohlenstoffatom oder ein Stickstoffatom ist; n eine ganze Zahl von 0 bis 2 ist;
eine gestrichelte Linie keine Bindung oder eine Einfachbindung ist;
R^1

ist {wobei D und E unabhängig voneinander eine Einfachbindung oder eine gegebenenfalls verzweigte C_1-C_6-Alkylengruppe bedeuten;
R^4 eine C_1-C_6-Alkylgruppe; -OR^6 (R^6 ist ein Wasserstoffatom, eine C_1-C_6-Alkylgruppe, eine gegebenenfalls substituierte C_6-C_{10}-Arylgruppe, eine gegebenenfalls substituierte C_3-C_8-Cycloalkylgruppe oder eine gegebenenfalls substituierte C_7-C_{12}-Aralkylgruppe), -SR^7 (R^7 ist eine C_1-C_6-Alkylgruppe, eine gegebenenfalls substituierte C_6-C_{10}-Arylgruppe, eine gegebenenfalls substituierte C_3-C_8-Cycloalkylgruppe oder eine gegebenenfalls substituierte C_7-C_{12}-Aralkylgruppe), -SOR^8 (R^8 ist eine gegebenenfalls substituierte C_6-C_{10}-Arylgruppe oder eine gegebenenfalls substituierte C_3-C_8-Cycloalkylgruppe), -SO_2R^9 (R^9 ist eine gegebenenfalls substituierte C_6-C_{10}-Arylgruppe oder eine gegebenenfalls substituierte C_3-C_8-Cycloalkylgruppe), -COR^{10} (R^{10} ist eine Hydroxylgruppe, eine C_1-C_6-Alkoxygruppe, eine gegebenenfalls substituierte C_6-C_{10}-Arylgruppe oder eine gegebenenfalls substituierte C_3-C_8-Cycloalkylgruppe), -NHR^{11} (R^{11} ist eine C_1-C_6-Alkylgruppe, eine gegebenenfalls substituierte C_6-C_{10}-Arylgruppe, eine gegebenenfalls substituierte C_3-C_8-Cycloalkylgruppe oder eine gegebenenfalls substituierte C_7-C_{12}-Aralkylgruppe), -$NHCOR^{12}$ (R^{12} ist eine C_1-C_6-Alkoxygruppe, eine gegebenenfalls substituierte C_6-C_{10}-Arylgruppe, eine gegebenenfalls substituierte C_3-C_8-Cycloalkylgruppe oder eine gegebenenfalls substituierte C_7-C_{12}-Aralkyloxygruppe), -$NHSO_2R^{13}$ (R^{13} ist eine C_1-C_6-Alkylgruppe, eine gegebenenfalls substituierte C_6-C_{10}-Arylgruppe, eine gegebenenfalls substituierte C_3-C_8-Cycloalkylgruppe, eine gegebenenfalls substituierte C_7-C_{12}-Aralkylgruppe oder eine gegebenenfalls substituierte 5- bis 10-gliedrige heterozyklische Gruppe), eine gegebenenfalls substituierte C_6-C_{10}-Arylgruppe, eine gegebenenfalls substituierte C_3-C_8-Cycloalkylgruppe, eine gegebenenfalls substituierte 5- bis 10-gliedrige heterozyklische Gruppe oder -$SiR^{14}R^{15}R^{16}$ ist (R^{14}, R^{15} und R^{16} bedeuten unabhängig voneinander eine C_1-C_6-Alkylgruppe);
R^5 -OR^{17}(R^{17} ist ein Wasserstoffatom, -$SiR^{22}R^{23}R^{24}$ (R^{22}, R^{23} und R^{24} bedeuten unabhängig voneinander eine C_1-C_6-Alkylgruppe), eine C_1-C_6-Alkylgruppe oder eine gegebenenfalls substituierte 5- bis 10-gliedrige heterozyklische Gruppe), -$OCOR^{18}$(R^{18} ist ein Wasserstoffatom, eine C_1-C_6-Alkylgruppe, eine C_1-C_6-Alkoxygruppe, eine Aminogruppe, eine C_1-C_6-Alkylaminogruppe, eine C_2-C_{12}-Dialkylaminogruppe oder eine C_2-C_7-Alkenylaminogruppe), -NHR^{19} (R^{19} ist ein Wasserstoffatom, eine C_1-C_6-Alkylgruppe oder eine gegebenenfalls substituierte C_7-C_{12}-Aralkylgruppe), -$NHCOR^{20}$(R^{20} ist ein Wasserstoffatom, eine C_1-C_6-Alkylgruppe, eine C_1-C_6-Halogenalkylgruppe, eine C_1-C_6-Alkoxygruppe, eine gegebenenfalls substituierte C_3-C_8-Cycloalkylgruppe, eine C_2-C_7-Carboxyalkyloxygruppe, eine C_2-C_7-Alkenyloxygruppe, eine gegebenenfalls substituierte C_6-C_{10}-Arylgruppe, eine gegebenenfalls substituierte C_6-C_{10}-Aryloxygruppe, eine C_3-C_9-Alkoxycarbonylalkoxygruppe, eine C_2-C_{12}-Dialkylaminogruppe oder eine gegebenenfalls substituierte C_7-C_{12}-Aralkyloxygruppe) oder -$NHSO_2R^{21}$ ist (R^{21} ist eine C_1-C_6-Alkylgruppe, eine C_1-C_6-Halogenalkylgruppe, eine C_2-C_7-Carboxyalkylgruppe, eine gegebenenfalls substituierte C_6-C_{10}-Arylgruppe, eine C_3-C_9-Alkoxycarbonylalkylgruppe oder eine gegebenenfalls substituierte C_7-C_{12}-Aralkylgruppe); und m 0 oder 1 ist;
jeder der 5- bis 10-gliedrigen heterozyklischen Gruppen unabhängig voneinander ausgewählt wird aus einem Furanring, einem Tetrahydrofuranring, einem Pyranring, einem Benzofuranring, einem Chromanring, einem Thiophenring, einem Benzothiophenring, einem Pyrrolring, einem Imidazolring, einem Pyrazolring, einem Triazolring, einem Pyridinring, einem Piperidinring, einem Pyrazinring, einem Piperazinring, einem Pyrimidinring, einem Indolring, einem Benzimidazolring, einem Purinring, einem Chinolinring, einem Phthalazinring, einem Chinazolinring, einem Cinnolinring, einem Oxazolring, einem Thiazolring und einem Morpholinring;
jeder der optionalen Substituenten unabhängig voneinander ausgewählt wird aus einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Halogenalkylgruppe, einer C_1-C_6-Alkoxygruppe, einer Hydroxylgruppe, einer Carboxylgruppe, einer C_2-C_7-Carboxyalkylgruppe, einer C_2-C_7-Carboxyalkyloxygruppe, einer C_2-C_7-Acylgruppe, einer C_2-C_7-Acyloxygruppe, einer C_2-C_7-Alkoxycarbonylgruppe, einer C_2-C_7-Alkoxycarbonyloxygruppe, einer C_8-C_{13}-Aralkyloxycarbonylgruppe, einer C_3-C_9-Alkoxycarboxyalkoxygruppe und einem Halogenatom};
R^2 ein Wasserstoffatom oder eine C_1-C_6-Alkylgruppe ist; und R^3 -$C(=NR^{25})NH_2$ (wobei R^{25} ein Wasserstoffatom oder eine Hydroxylgruppe ist) oder -NH_2 ist; vorausgesetzt, dass R^3 -$C(=NR^{25})NH_2$ (R^{25} ist wie oben definiert) ist, wenn A ein Stickstoffatom ist, oder ein Salz oder Hydrat davon;
mit der Maßgabe, dass falls der Substituent R^2 ein Wasserstoffatom darstellt, die Gruppe "D" eine Einfachbindung darstellt und der Index n 1 oder 2 ist, keiner der Substituenten R^4 oder R^5 eine Gruppe darstellt, die einen Aminosulfonylrest einschließt.

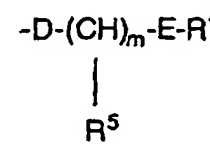
2. Verbindung gemäß Anspruch 1, wobei A ein Kohlenstoffatom ist.

3. Verbindung gemäß Anspruch 1 oder 2, wobei n 1 oder 2 ist; R^1



ist {wobei D und E unabhängig voneinander eine Einfachbindung oder eine gegebenenfalls verzweigte C_1-C_6-Alkylengruppe darstellen;
R^4 eine C_1-C_6-Alkylgruppe; -OR^6 (R^6 ist eine C_1-C_6-Alkylgruppe; eine C_6-C_{10}-Arylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Alkoxygruppe, einem Halogenatom, einer Hydroxylgruppe, einer Carboxylgruppe, einer C_2-C_7-Alkoxycarbonylgruppe, einer C_2-C_7-Carboxyalkylgruppe, einer C_2-C_7-Acylgruppe, einer C_2-C_7-Acyloxygruppe, einer C_2-C_7-Alkoxycarbonyloxygruppe, einer C_3-C_9-Alkoxycarbonylalkoxygruppe und eine Benzyloxycarbonylgruppe besteht; oder einer C7-C12-Aralkylgruppe ist, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Alkoxygruppe, einem Halogenatom, einer Hydroxylgruppe, einer Carboxylgruppe, einer C_2-C_7-Alkoxycarbonylgruppe, einer C_2-C_7-Carboxyalkylgruppe, einer C_2-C_7-Acylgruppe, einer C_2-C_7-Acyloxygruppe, einer C_2-C_7-Alkoxycarbonyloxygruppe, einer C_3-C_9-Alkoxycarbonylalkoxygruppe und einer Benzyloxycarbonylgruppe besteht); -SR^7 (R^7 ist eine C_1-C_6-Alkylgruppe; eine C_6-C_{10}-Arylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Alkoxygruppe, einem Halogenatom, einer Hydroxylgruppe, einer Carboxylgruppe, einer C_2-C_7-Alkoxycarbonylgruppe, einer C_2-C_7-Carboxyalkylgruppe, einer C_2-C_7-Acylgruppe, einer C_2-C_7-Acyloxygruppe, einer C_2-C_7-Alkoxycarbonyloxygruppe, einer C_3-C_9-Alkoxycarbonylalkoxygruppe und einer Benzyloxycarbonylgruppe besteht; oder eine C_7-C_{12}-Aralkylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Alkoxygruppe, einem Halogenatom, einer Hydroxylgruppe, einer Carboxylgruppe, einer C_2-C_7-Alkoxycarbonylgruppe, einer C_2-C_7-Carboxyalkylgruppe, einer C_2-C_7-Acylgruppe, einer C_2-C_7-Acyloxygruppe, einer C_2-C_7-Alkoxycarbonyloxygruppe, einer C_3-C_9-Alkoxycarbonylalkoxygruppe und einer Benzyloxycarbonylgruppe besteht); -COOH; eine C_6-C_{10}-Arylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Alkoxygruppe, einem Halogenatom, einer Hydroxylgruppe, einer Carboxylgruppe, einer C_2-C_7-Alkoxycarbonylgruppe, einer C_2-C_7-Carboxyalkylgruppe, einer C_2-C_7-Acylgruppe, einer C_2-C_7-Acyloxygruppe, einer C_2-C_7-Alkoxycarbonyloxygruppe, einer C_3-C_9-Alkoxycarbonylalkoxygruppe und einer Benzyloxycarbonylgruppe besteht; eine C_3-C_8-Cycloalkylgruppe; oder -$SiR^{14}R^{15}R^{16}$ ist (R^{14}, R^{15} und R^{16} bedeuten unabhängig voneinander eine C_1-C_6-Alkylgruppe);
R^5 -OH, -$OCOR^{18}$ (R^{18} ist eine C_1-C_6-Alkoxygruppe oder eine C_2-C_7-Alkenylaminogruppe), -NH_2, -$NHCOR^{20}$ (R^{20} ist eine C_1-C_6-Alkoxygruppe, einer C_6-C_{10}-Aryloxygruppe, eine C_3-C_9-Alkoxycarbonylalkoxygruppe, eine C_2-C_{12}-Dialkylaminogruppe oder eine C_7-C_{12}-Aralkyloxygruppe) oder -$NHSO_2R^{21}$ ist (R^{21} ist eine C_1-C_6-Alkylgruppe, eine C_2-C_7-Carboxyalkylgruppe, eine C_6-C_{10}-Arylgruppe, eine C_3-C_9-Alkoxycarbonylalkylgruppe oder eine C_7-C_{12}-Aralkylgruppe); und m 0 oder 1 ist }; und
R^2 ein Wasserstoffatom ist.

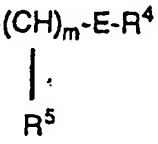
4. Verbindung gemäß Anspruch 1 oder 2, wobei n 1 ist; R^1



ist {wobei D und E unabhängig voneinander eine Einfachbindung oder eine gegebenenfalls verzweigte C_1-C_6-Alkylengruppe darstellen;

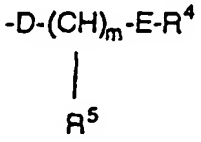
R^4 eine C_1-C_6-Alkylgruppe; -OR^6 (R^6 ist eine C_6-C_{10}-Arylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C_1-C_6-Alkylgruppe, einem Halogenatom, einer Carboxylgruppe, einer C_2-C_7-Carboxyalkylgruppe und einer Benzyloxycarbonylgruppe oder C_7-C_{12}-Aralkylgruppe) besteht; -SR^7 (R^7 ist eine C_1-C_6-Alkylgruppe); eine C_6-C_{10}-Arylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C_1-C_6-Alkylgruppe, einem Halogenatom, einer Carboxylgruppe, einer C_2-C_7-Carboxyalkylgruppe und einer Benzyloxycarbonylgruppe besteht; oder eine C_3-C_6-Cycloalkylgruppe ist;
R^5 -OH, NH_2, -$NHCOR^{20}$ (R^{20} ist eine C_1-C_6-Alkoxygruppe oder eine C_7-C_{12}-Aralkyloxygruppe) oder -$NHSO_2R^{21}$ ist (R^{21} ist eine C_1-C_6-Alkylgruppe oder eine C_6-C_{10}-Arylgruppe); und m 1 ist}; und
R^2 ein Wasserstoffatom ist.

5. Verbindung gemäß Anspruch 1 oder 2, wobei n 1 ist; R^1



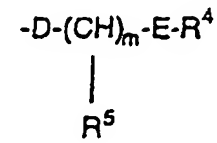
ist {wobei D eine Einfachbindung ist; E eine Einfachbindung oder eine C_1-C_6-Alkylengruppe ist;
R^4 eine C_1-C_6-Alkylgruppe; -OR^6 (R^6 ist eine C_6-C_{10}-Arylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C_1-C_6-Alkylgruppe, einem Halogenatom, einer Carboxylgruppe, einer C_2-C_7-Carboxyalkylgruppe und einer Benzyloxycarbonylgruppe oder einer C_7-C_{12}-Aralkylgruppe besteht); -SR^7 (R^7 ist eine C_1-C_6-Alkylgruppe); eine C_6-C_{10}-Arylgruppe, die mit mindestens einem oder mehreren Substituenten substituiert sein kann, die aus der Gruppe ausgewählt werden, die aus einer C_1-C_6-Alkylgruppe, einem Halogenatom, einer Carboxylgruppe, einer C_2-C_7-Carboxyalkylgruppe und einer Benzyloxycarbonylgruppe besteht; oder eine C_3-C_6-Cycloalkylgruppe ist;
R^5 -NH_2, -$NHCOR^{20}$ (R^{20} ist eine C_1-C_6-Alkoxygruppe oder eine C_7-C_{12}-Aralkyloxygruppe) oder -$NHSO_2R^{21}$ ist (R^{21} ist eine C_1-C_6-Alkylgruppe oder eine C_6-C_{10}-Arylgruppe); und m 1 ist}; und
R^2 ein Wasserstoffatom ist.

6. Verbindung gemäß Anspruch 1, wobei A ein Kohlenstoffatom ist; n 1 ist; R^1



ist {wobei D eine Einfachbindung ist; E eine Einfachbindung oder eine C_1-C_3-Alkylengruppe ist; R^4 eine C_3-C_6-Alkylgruppe), oder -OR^6 ist (R^6 ist eine C_1-C_6-Alkylgruppe, eine Phenylgruppe oder eine C_3-C_6-Cycloalkylgruppe);
R^5 -OH,-NHR^{19} (R^{19} ist ein Wasserstoffatom), -$NHCOR^{20}$ (R^{20} ist eine C_1-C_6-Alkoxygruppe) oder -$NHSO_2R^{21}$ ist (R^{21} ist eine C_1-C_3-Alkylgruppe); und m 1 ist}; und
R^2 ein Wasserstoffatom ist.

7. Verbindung gemäß Anspruch 1 oder 2, wobei n 1 ist; R^1



ist {D ist eine Einfachbindung; E ist eine Einfachbindung oder eine C_1-C_6-Alkylengruppe; R^4 ist eine C_1-C_6-Alkylgruppe; R^5 ist -$NHCOR^{20}$ (R^{20} ist eine C_1-C_6-Alkoxygruppe); und m ist 1};

R^2 ein Wasserstoffatom ist; und
R^3 -C(=NR^{25})NH_2 ist (R^{25} ist ein Wasserstoffatom oder eine Hydroxylgruppe).

8. Trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl)prolyl]aminomethylcyclohexancarboxamidoxim oder ein Salz oder Hydrat davon.

9. Pharmazeutische Zusammensetzung umfassend eine Verbindung wie in einem der Ansprüche 1 bis 8 beansprucht und einen pharmazeutisch akzeptablen Träger dafür.

10. Verwendung einer Verbindung wie in einem der Ansprüche 1 bis 8 beansprucht zur Herstellung eines Medikaments, das als Proteaseinhibitor wirksam ist.

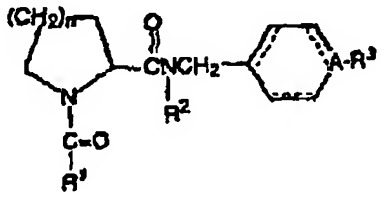
11. Verbindung gemäß einem der Ansprüche 1 bis 8 zur Verwendung als Medikament.

12. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 8 zur Herstellung eines gerinnungshemmenden Medikaments.

13. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 8 zur Herstellung eines Medikaments zur Behandlung von Pankreatitis.

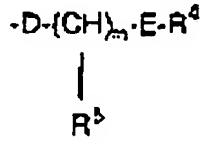
Revendications

1. Dérivé de la prolinamide représenté par la formule (I):



(I)

dans laquelle A est un atome de carbone ou un atome d'azote ;
n est un entier de 0 à 2 ; une ligne pointillée représente une absence de liaison ou une simple liaison ;
R^1 est



{dans laquelle D et E indiquent séparément une simple liaison ou un groupe alkylène en C_1 à C_6 qui peut être facultativement ramifié ;

R^4 représente un groupe alkyle en C_1 à C_6; -OR^6 (R^6 est un atome d'hydrogène, un groupe alkyle en C_1 à C_6, un groupe aryle en C_6 à C_{10} que l'on peut facultativement substituer, un groupe cycloalkyle en C_3 à C_8 que l'on peut facultativement substituer ou un groupe aralkyle en C_7 à C_{12} que l'on peut facultativement substituer), -SR^7 (R^7 représente un groupe alkyle en C_1 à C_6, un groupe aryle en C_6 à C_{10} que l'on peut facultativement substituer, un groupe cycloalkyle en C_3 à C_8 que l'on peut facultativement substituer ou un groupe aralkyle en C_7 à C_{12} que l'on peut facultativement substituer), -SOR^8 (R^8 est un groupe aryle en C_6 à C_{10} que l'on peut facultativement substituer ou un groupe cycloalkyle en C_3 à C_8 que l'on peut facultativement substituer), -SO_2R^9 (R^9 est un groupe aryle en C_6 à C_{10} que l'on peut facultativement substituer ou un groupe cycloalkyle en C_3 à C_8 que l'on

peut facultativement substituer), -COR^{10} (R^{10} est un groupe hydroxyle, un groupe alcoxyle en C_1 à C_6, un groupe aryle en C_6 à C_{10} que l'on peut facultativement substituer ou un groupe cycloalkyle en C_3 à C_8 que l'on peut facultativement substituer), -NHR^{11} (R^{11} est un groupe alkyle en C_1 à C_6, un groupe aryle en C_6 à C_{10} que l'on peut facultativement substituer, un groupe cycloalkyle en C_3 à C_8 que l'on peut facultativement substituer ou groupe aralkyle en C_7 à C_{12} que l'on peut facultativement substituer), -$NHCOR^{12}$ (R^{12} est un groupe alcoxyle en C_1 à C_6, un groupe aryle en C_6 à C_{10} que l'on peut facultativement substituer, un groupe cycloalkyle en C_3 à C_8 que l'on peut facultativement substituer ou un groupe aralkyloxy en C_7 à C_{12} que l'on peut facultativement substituer), -$NHSO_2R^{13}$ (R^{13} est un groupe alkyle en C_1 à C_6, un groupe aryle en C_6 à C_{10} que l'on peut facultativement substituer, un groupe cycloalkyle en C_3 à C_8 que l'on peut facultativement substituer, un groupe aralkyle en C_7 à C_{12} que l'on peut facultativement substituer, ou un groupe hétérocyclique de 5 à 10 chaînons que l'on peut facultativement substituer), un groupe aryle en C_6 à C_{10} que l'on peut facultativement substituer, un groupe cycloalkyle en C_3 à C_8 que l'on peut facultativement substituer, un groupe hétérocyclique de 5 à 10 chaînons que l'on peut facultativement substituer ou -$SiR^{14}R^{15}R^{16}$(R^{14}, R^{15}, et R^{16} représentent séparément un groupe alkyle en C_1 à C_6);

R^5 est un -OR^{17}(R^{17} est un atome d'hydrogène, -$SiR^{22}R^{23}R^{24}$ (R^{22}, R^{23}, et R^{24} représentent séparément un groupe alkyle en C_1 à C_6), un groupe alkyle en C_1 à C_6, ou un groupe hétérocyclique de 5 à 10 chaînons que l'on peut facultativement substituer), -$OCOR^{18}$ (R^{18} est un atome d'hydrogène, un groupe alkyle en C_1 à C_6, un groupe alcoxyle en C_1 à C_6, un groupe aminé, un groupe alkylamine en C_1 à C_6, un groupe dialkylamine en C_2 à C_{12} ou un groupe alkénylamine en C_2 à C_7), -NHR^{19} (R^{19} est un atome d'hydrogène, un groupe alkyle en C_1 à C_6 ou un groupe aralkyle en C_7 à C_{12} que l'on peut facultativement substituer), -$NHCOR^{20}$ (R^{20} est un atome d'hydrogène, un groupe alkyle en C_1 à C_6, un groupe alkyle halogéné en C_1 à C_6, un groupe alcoxyle en C_1 à C_6, un groupe cycloalkyle en C_3 à C_8 que l'on peut facultativement substituer, un groupe carboxyalkyloxy en C_2 à C_7, un groupe alkényloxy en C_2 à C_7, un groupe aryle en C_6 à C_{10} que l'on peut facultativement substituer, un groupe aryloxy en C_6 à C_{10} que l'on peut facultativement substituer, un groupe alcoxycarbonylalcoxy en C_3 à C_9, un groupe dialkylamine en C_2 à C_{12} ou un groupe aralkyloxy en C_7 à C_{12} que l'on peut facultativement substituer) ou -$NHSO_2R^{21}$ (R^{21} est un groupe alkyle en C_1 à C_6, un groupe alkyle halogéné en C_1 à C_6, un groupe carboxyalkyle en C_2 à C_7, un groupe aryle en C_6 à C_{10} que l'on peut facultativement substituer, un groupe alcoxycarbonylalkyle en C_3 à C_9 ou un groupe aralkyle en C_7 à C_{12} que l'on peut facultativement substituer) ; et m a la valeur 0 ou 1 ;

chacun desdits groupes hétérocycliques de 5 à 10 chaînons est choisi indépendamment parmi un noyau furanne, un noyau tétrahydrofuranne, un noyau pyranne, un noyau benzofuranne, un noyau chromanne, un noyau thiophène, un noyau benzothiophène, un noyau pyrrole, un noyau imidazole, un noyau pyrazole, un noyau triazole, un noyau pyridine, un noyau pipéridine, un noyau pyrazine, un noyau pipérazine, un noyau pyrimidine, un noyau indole, un noyau benzimidazole, un noyau purine, un noyau quinoline, un noyau phtalazine, un noyau quinazoline, un noyau cinniline, un noyau oxazole, un noyau thiazole et un noyau morpholine ;

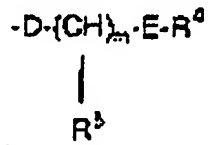
on choisit chacun desdits substituants éventuels parmi un groupe alkyle en C_1 à C_6, un groupe alkyle halogéné en C_1 à C_6, un groupe alcoxyle en C_1 à C_6, un groupe hydroxyle, un groupe carboxyle, un groupe carboxyalkyle en C_2 à C_7, un groupe carboxyalkyloxy en C_2 à C_7, un groupe acyle en C_2 à C_7, un groupe acyloxy en C_2 à C_7, un groupe alcoxycarbonyle en C_2 à C_7, un groupe alcoxycarbonyloxy en C_2 à C_7, un groupe aralkyloxycarbonyle en C_8 à C_{13}, un groupe alcoxycarboxyalcoxyle en C_3 à C_9 et un atome d'halogène) ;

R^2 est un atome d'hydrogène ou un groupe alkyle en C_1 à C_6; et R^3 est représenté par -$C(=NR^{25})NH_2$ (dans lequel R^{25} est un atome d'hydrogène ou un groupe hydroxyle) ou -NH_2; à la condition que R^3 soit représenté par -$C(=NR^{25})NH_2$ (R^{25} est défini comme ci-dessus) lorsque A est un atome d'azote, ou un sel ou un hydrate qui en dérivent ;

à la condition que si le substituant R^2 représente un atome d'hydrogène, le groupe « D » représente une simple liaison, et l'index n a la valeur 1 ou 2, alors aucun des substituants R^4 ou R^5 ne représente un groupe comportant un groupe fonctionnel aminosulfonyle.

2. Composé selon la revendication 1, dans lequel A est un atome de carbone.

3. Composé selon la revendication 1 ou la revendication 2, dans lequel n a la valeur 1 ou 2 ; R^1 est représenté par



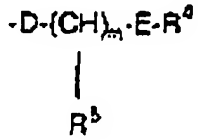
{dans laquelle D et E indiquent séparément une simple liaison ou ou un groupe alkylène ramifié en C_1 à C_6;

R^4 est un groupe alkyle en C_1 à C_6 ; -OR^6(R^6 est un groupe alkyle en C_1 à C_6 ; un groupe aryle en C_6 à C_{10} qui peuvent être substitués avec au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C_1 à C_6, d'un groupe alcoxyle en C_1 à C_6, d'un atome d'halogène, d'un groupe hydroxyle, d'un groupe carboxyle, d'un groupe alcoxycarbonyle en C_2 à C_7, d'un groupe carboxyalkyle en C_2 à C_7, d'un groupe acyle en C_2 à C_7, d'un groupe acyloxy en C_2 à C_7, d'un groupe alcoxycarbonyloxy en C_2 à C_7, d'un groupe alcoxycarbonylalcoxyle en C_3 à C_9 et d'un groupe benzyloxycarbonyle ; ou un groupe aralkyle en C_7 à C_{12} qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C_1 à C_6, d'un groupe alcoxyle en C_1 à C_6, d'un atome d'halogène, d'un groupe hydroxyle, d'un groupe carboxyle, d'un groupe alcoxycarbonyle en C_2 à C_7, d'un groupe carboxyalkyle en C_2 à C_7, d'un groupe acyle en C_2 à C_7, d'un groupe acyloxy en C_2 à C_7, d'un groupe alcoxycarbonyloxy en C_2 à C_7, d'un groupe alcoxycarbonylalcoxyle en C_3 à C_9, et d'un groupe benzyloxycarbonyle) ; -SR^7 (R^7 est un groupe alkyle en C_1 à C_6 ; un groupe aryle en C_6 à C_{10} qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C_1 à C_6, d'un groupe alcoxyle en C_1 à C_6, d'un atome d'halogène, d'un groupe hydroxyle, d'un groupe carboxyle, d'un groupe alcoxycarbonyle en C_2 à C_7, d'un groupe carboxyalkyle en C_2 à C_7, d'un groupe acyle en C_2 à C_7, d'un groupe acyloxy en C_2 à C_7, d'un groupe alcoxycarbonyloxy en C_2 à C_7, d'un groupe alcoxycarbonylalcoxyle en C_3 à C_9, et d'un groupe benzyloxycarbonyle ; ou un groupe aralkyle en C_7 à C_{12} qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C_1 à C_6, d'un groupe alcoxyle en C_1 à C_6, d'un atome d'halogène, d'un groupe hydroxyle, d'un groupe carboxyle, d'un groupe alcoxycarbonyle en C_2 à C_7, d'un groupe carboxyalkyle en C_2 à C_7, d'un groupe acyle en C_2 à C_7, d'un groupe acyloxy en C_2 à C_7, d'un groupe alcoxycarbonyloxy en C_2 à C_7, d'un groupe alcoxycarbonylalcoxyle en C_3 à C_9, et d'un groupe benzyloxycarbonyle) ; -COOH ; un groupe aryle en C_6 à C_{10} qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C_1 à C_6, d'un groupe alcoxyle en C_1 à C_6, d'un atome d'halogène, d'un groupe hydroxyle, d'un groupe carboxyle, d'un groupe alcoxycarbonyle en C_2 à C_7, d'un groupe carboxyalkyle en C_2 à C_7, d'un groupe acyle en C_2 à C_7, d'un groupe acyloxy en C_2 à C_7, d'un groupe alcoxycarbonyloxy en C_2 à C_7, d'un groupe alcoxycarbonylalcoxyle en C_3 à C_9 et d'un groupe benzyloxycarbonyle ; d'un groupe cycloalkyle en C_3 à C_8 ; ou -$SiR^{14}R^{15}R^{16}$ (R^{14}, R^{15}, et R^{16} indiquent séparément un groupe alkyle en C_1 à C_6) ;

R^5 est -OH, -$OCOR^{18}$ (R^{18} est un groupe alcoxyle en C_1 à C_6 ou un groupe alkénylamine en C_2 à C_7), -NH_2, -$NHCOR^{20}$ (R^{20} est un groupe alcoxyle en C_1 à C_6, un groupe aryloxy en C_6 à C_{10}, un groupe alcoxycarbonylalcoxyle en C_3 à C_9, un groupe dialkylamine en C_2 à C_{12} ou un groupe aralkyloxy en C_7 à C_{12}) ou -$NHSO_2R^{21}$ (R^{21} est un groupe alkyle en C_1 à C_6, un groupe carboxyalkyle en C_2 à C_7, un groupe aryle en C_6 à C_{10}, un groupe alcoxycarbonylalkyle en C_3 à C_9 ou un groupe aralkyle en C_7 à C_{12}); et m a la valeur 0 ou 1} ; et

R^2 est un atome d'hydrogène.

4. Composé selon la revendication 1 ou la revendication 2, dans lequel n a la valeur 1 ; R^1 est



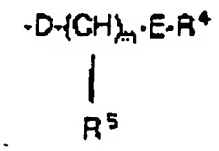
{dans laquelle D et E indiquent séparément une simple liaison ou un groupe alkylène en C_1 à C_6 éventuellement ramifié ;

R_4 est un groupe alkyle en C_1 à C_6 ; -OR^6 (R^6 est un groupe aryle en C_6 à C_{10} qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C_1 à C_6, d'un atome d'halogène, d'un groupe carboxyle, d'un groupe carboxyalkyle en C_2 à C_7 et d'un groupe benzyloxycarbonyle ou d'un groupe aralkyle en C_7 à C_{12}) ; -SR^7 (R^7 est un groupe alkyle en C_1 à C_6) ; un groupe aryle en C_6 à C_{10} qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C_1 à C_6, d'un atome d'halogène, d'un groupe carboxyle, d'un groupe carboxyalkyle en C_2 à C_7 et d'un groupe benzyloxycarbonyle ; ou un groupe cycloalkyle en C_3 à C_6 ;

R^5 est représenté par -OH, NH_2, -$NHCOR^{20}$ (R^{20} est un groupe alkyle en C_1 à C_6 ou un groupe aralkyloxy en C_7 à C_{12}) ou -$NHSO_2R^{21}$ (R^{21} est un groupe alkyle en C_1 à C_6 ou un groupe aryle en C_6 à C_{10}) et m a la valeur 1} ; et

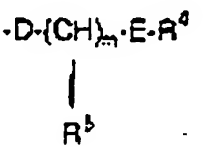
R^2 est un atome d'hydrogène.

5. Composé selon la revendication 1 ou la revendication 2, dans lequel n a la valeur 1 ; R^1 est



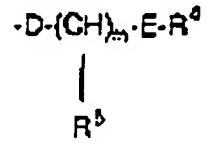
{dans laquelle D est une simple liaison ; E est une simple liaison ou un groupe alkylène en C_1 à C_6 ;
R_4 est un groupe alkyle en C_1 à C_6 ; $-OR^6$ (R_6 est un groupe aryle en C_6 à C_{10} qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C_1 à C_6, d'un atome d'halogène, d'un groupe carboxyle, d'un groupe carboxyalkyle en C_2 à C_7 et d'un groupe benzyloxycarbonyle ou d'un groupe aralkyle en C_7 à C_{12}); $-SR^7$ (R^7 est un groupe alkyle en C_1 à C_6) ; un groupe aryle en C_6 à C_{10} qui peut être substitué par au moins un ou plusieurs substituants choisis parmi le groupe composé d'un groupe alkyle en C_1 à C_6, d'un atome d'halogène, d'un groupe carboxyle, d'un groupe carboxyalkyle en C_2 à C_7 et d'un groupe benzyloxycarbonyle ; ou d'un groupe cycloalkyle en C_3 à C_6 ;
R^5 est représenté par $-NH_2$, $-NHCOR^{20}$ (R^{20} est un groupe alcoxyle en C_1 à C_6 ou un groupe aralkyloxy en C_7 à C_{12}) ou $-NHSO_2R^{21}$ (R^{21} est un groupe alkyle en C_1 à C_6 ou un groupe aryle en C_6 à C_{10}) ; et m a la valeur 1} ; et
R^2 est un atome d'hydrogène.

6. Composé selon la revendication 1, dans lequel A est un atome de carbone ; n a la valeur 1 ; R^1 est



{dans laquelle D est une simple liaison ; E est une simple liaison ou un groupe alkylène en C_1 à C_3 ; R^4 est un groupe alkyle en C_3 à C_6), $-OR^6$ (R^6 est un groupe alkyle en C_1 à C_6, un groupe phényle, ou un groupe cycloalkyle en C_3 à C_6 ; R^5 est représenté par -OH, $-NHR^{19}$ (R^{19} est un atome d'hydrogène), $-NHCOR^{20}$ (R^{20} est un groupe alcoxyle en C_1 à C_6) ou $-NHSO_2R^{21}$ (R^{21} est un groupe alkyle en C_1 à C_3); et m a la valeur 1} ; et
R^2 est un atome d'hydrogène.

7. Composé selon la revendication 1 ou la revendication 2, dans lequel n a la valeur 1 ; R^1 est



{D est une simple liaison ; E est une simple liaison ou un groupe alkylène en C_1 à C_6 ; R^4 est un groupe alkyle en C_1 à C_6 ; R^5 est $-NHCOR^{20}$ (R^{20} est un groupe alcoxyle en C_1 à C_6) ; et m a la valeur 1} ;
R^2 est un atome d'hydrogène ; et
R^3 est représenté par $-C(=NR^{25})NH_2$ (R^{25} est un atome d'hydrogène ou un groupe hydroxyle).

8. Trans-4-[(S)-N-((R)-2-éthoxycarbonylamino-4,4-diméthylpentanoyl)prolyl] aminométhylcyclohexanecarboxamidoxime ou un sel ou un hydrate qui en dérivent.

9. Composition pharmaceutique comportant un composé selon l'une quelconque des revendications 1 à 8 et de ce fait un support pharmaceutiquement acceptable.

10. Utilisation d'un composé selon l'une quelconque des revendications 1 à 8 pour la fabrication d'un médicament efficace comme inhibiteur de protéase.

11. Composé selon l'une quelconque des revendications 1 à 8 pour une utilisation comme médicament.

12. Utilisation d'un composé selon l'une quelconque des revendications 1 à 8 pour la fabrication d'un médicament anticoagulant.

13. Utilisation d'un composé selon l'une quelconque des revendications 1 à 8 pour la fabrication d'un médicament pour le traitement de la pancréatite.